Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Maraviroc

Proprietary Product Name: Celsentri

Sponsor: ViiV Healthcare Pty Ltd

May 2013

TGA Health Safety Regulation

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Contents

I. Introduction to product submission

Submission details

Type of Submission:	Major variation – extension of indications
Decision:	Approved
Date of Decision:	22 August 2012
Active ingredient:	Maraviroc
Product Name:	Celsentri
Sponsor's Name and Address:	ViiV Healthcare Pty Ltd Level 4, 436 Johnston street, Abbotsford VIC 3067
Dose form:	Tablet
Strengths:	150 mg and 300 mg
Containers:	Bottle, blister pack
Pack sizes:	180 tablets (bottle); 60 tablets (blister)
Approved Therapeutic use:	Celsentri, in combination with other antiretroviral medicinal products, is indicated for adult patients infected with only CCR5-tropic HIV-1. The use of other active agents with Celsentri is associated with a greater likelihood of treatment response.
Route of administration:	Oral
Dosage (abbreviated):	Adults: 150 mg, 300 mg or 600 mg twice daily depending on interactions with co-administered antiretroviral therapy and other medicinal products.
ARTG Numbers:	137330, 137332, 137331, 137329

Product background

An essential step in the human immunodeficiency virus (HIV) replication cycle is attachment to both the helper T cell ($CD4^+$) receptor and one of the chemokine co-receptors (CC), either CCR5 or CXCR4.[1] Maraviroc is a selective CCR5 co-receptor antagonist, active *in vitro* against a wide range of clinical isolates including those resistant to existing drug classes.

[1] CCR5 and CXCR4 are also referred to as R5 and X4, respectively, in this report.

Celsentri was first registered on the Australian Register of Therapeutic Goods (ARTG) in February 2008 for treatment experienced adult patients, as follows:

Celsentri, in combination with other antiretroviral medicinal products, is indicated for treatment-experienced adult patients infected with only CCR5-tropic HIV-1.

This indication is based on analyses of plasma HIV-1 RNA levels and $CD4^+$ cell counts at 24 weeks in two double-blind, placebo-controlled trials in treatment-experienced patients with clinically advanced disease resistant to three or four classes of antiretrovirals.

The use of other active agents with CELSENTRI is associated with a greater likelihood of treatment response.

This AusPAR describes the application by ViiV Healthcare Pty Ltd (the sponsor) to extend the approved indications for Celsentri to include treatment naïve patients. The requested (amended) indications are:

> *Celsentri, in combination with other antiretroviral medicinal product, is indicated for adult patients infected with CCR5-tropic HIV-1.*
>
> *The use of other active agents with CELSENTRI is associated with a greater likelihood of treatment response.*

Regulatory status

Celsentri received initial ARTG Registration on 4 February 2008.

At the time of the current application, a similar application and data package were submitted to Canada, the European Union (EU) and the United States (US). Canada and the US approved the indication for treatment naïve patients. Both have included in the *Indication*, a statement concerning the risk of development of viral resistance to lamivudine and emergence of CXCR4 tropic HIV-1 and instruction to use highly sensitive tropism testing prior to initiating therapy. The application was rejected in the EU.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Background and rationale

The rationale for development of maraviroc was the finding that individuals who are heterozygous for the Δ32 mutant CCR5 allele with fewer functional CCR5 receptors, have lower serum viral loads (VLs), a better response to highly active antiretroviral therapy (HAART) and delayed progression to acquired immunodeficiency syndrome (AIDS) or death.

CCR5 is the co-receptor which predominates during the early stages of HIV-1 infection. Between 85% and 90% of treatment naïve patients reportedly have only CCR5-tropic HIV-1 detectable. Thus, a CCR5 antagonist was considered to have the potential to provide benefit to a sizeable proportion of the treatment naïve population.

Maraviroc is currently indicated for treatment experienced adults, based on clinical trial data up to 24 weeks. The proposed indication would extend the use of maraviroc to treatment naïve patients.

The application is based on the:

- 48 Week and 96 Week results of pivotal Study A4001026[2] for treatment naïve patients
- 48 Week results from the two pivotal Phase III Studies A4001027 and A4001028 in treatment experience patients infected with CCR5-tropic HIV-1, and
- 48 Week results for supportive Study A4001029 examining the safety of maraviroc in treatment experienced patients infected with non-CCR5 tropic or non-phenotypable HIV-1.

The sponsor provided assurance that these studies were performed in compliance with Good Clinical Practice requirements. Studies A4001026, A4001027, A2001028 and A4001029 are summarised in Tables 1, 2, 3 and 4, respectively, below.

[2] Also known as the Maraviroc versus Efavirenz in Treatment naïve patients (MERIT) study.

Table 1 Summary of Study A4001026

Investigator, Country, Year	Design/objectives	Participants	Efficacy results	Safety results
James M Goodrich Conducted in Argentina (9), Australia (10), Belgium (4), Canada (17), Italy (8), Mexico (4), Netherlands (1), Poland (7), South Africa (13), Switzerland (7), UK (7), US including Puerto Rico (40) November 2004 to March 2008. Maraviroc QD arm discontinued January 2006	Phase IIb/III, 96 week, multinational, multi-centre, double blind, randomised (1:1:1) study. Primary objective: to assess non-inferiority of response at Week 48 in terms of plasma VL < 400 copies/mL and < 50 copies/mL for maraviroc compared to efavirenz each in combination with zidovudine/lamivudine in antiretroviral-naïve, CCR5-tropic HIV-1 infected patients. Similar assessments at Week 24 and Week 96 were secondary objectives. Non-inferiority was shown if the lower bound (LB) of the one sided 97.5% CI for the difference in percentage with specified response was above -10%. Treatments were: Maraviroc 300 mg QD (discontinued early for lack of efficacy), maraviroc 300 mg BID, and efavirenz 600 mg QD, each with zidovudine 300 mg BID and lamivudine 150 mg BID. Groups were stratified by screening VL (<100,000 or ≥100,000 copies/mL) and by geographic location (Northern versus Southern Hemisphere). Primary analysis at 48 Weeks was adjusted for randomisation strata.	Treatment naïve participants ≥16 years of age, infected with CCR5-tropic HIV-1 with VL ≥ 2000 copies/mL. Patients: Screened: 1730, Randomised: 740 Maraviroc BID: 360 Efavirenz QD: 361 Mean age: approx 37 years, range 18–77 years White: approx. 55%, Black: 35%, Hispanic: approx. 20%	Non-inferiority shown for VL < 400 copies/mL for the FAS. LB of one sided 97.5% CI: -9.5%. Non-inferiority not shown for VL < 50 copies/mL for the FAS as the LB of the CI was -10.9%. Non-inferiority was not shown for PP sets for VL < 400 copies/mL or < 50 copies/mL The Week 96 secondary analysis results failed to show non-inferiority for both VLs and both analysis populations. Results based on enhanced sensitivity Trofile assay[3] were included.	Safety to 96 weeks: Approximately 94% of both groups reported adverse events (AE). Treatment related AEs: 65% for maraviroc, 79% for efavirenz. Deaths on study drug or within 28 days of discontinuation: maraviroc 2; efavirenz 3. Two deaths were considered related to the study drug, each in the maraviroc group: one case of nasopharyngeal cancer, reported on Day 502 and one case of diffuse large B-cell lymphoma, reported Day 268. Serious AEs considered treatment related: maraviroc 2.8%; efavirenz 4.2%. Permanent discontinuation due to treatment related AEs: maraviroc 4.2%; efavirenz 13.0%.

[3] The Trofile co-receptor tropism assay identifies which co-receptor (CCR5 or CXCR4, or both) a patient's HIV strain uses to enter T cells. The enhanced sensitivity Trofile assay improves on the sensitivity of the original assay.

Table 2 Summary of Study A4001027

Investigator, Country, Year	Design/objectives	Participants	Efficacy results	Safety results
Multiple centres in North America Multiple investigators November 2004 to April 2007	A multicentre, double-blind, placebo-controlled trial, randomised 2:2:1 to treatment with maraviroc 300 mg once daily (QD) or maraviroc 300 mg twice daily (BID) in combination with optimised background therapy (OBT) versus matching placebo with OBT, to investigate superiority of maraviroc versus placebo. Primary objective: To assess whether maraviroc added to OBT provides an additional reduction in plasma HIV-1 ribonucleic acid (RNA) compared to OBT alone, as measured by the difference between each of the two maraviroc regimens versus the placebo regimen in the mean changes from baseline in plasma HIV-1 RNA at Week 48. If the 2-sided 97.5% confidence interval (CI) was completely to the left side and excluded zero, the superiority of maraviroc over placebo was concluded. NB: in case of concomitant protease inhibitor use except tipranavir, and/or delavirdine use, the maraviroc dose was reduced from 300 mg to 150 mg.	CCR5 tropic HIV-1 infected patients ≥ 16 years of age with ≥ 6 months of prior treatment with at least 1 agent from 3 antiretroviral drug classes or documented multi-class resistance, with plasma VL ≥ 5,000 copies/mL Screened: 1816 Randomised: 601 Treated: 585: Maraviroc QD: 232; Maraviroc BID: 235; Placebo: 118 Males: approx. 90%, the majority between 35 and 54 years of age and more than 80% were White.	Superiority was shown in the pre-defined terms. Adjusted mean changes from baseline in VL $\log_{10}$ copies/mL were: Maraviroc QD - 1.656 Maraviroc BID - 7.824 Placebo - 0.803. The treatment differences (95% CI) were: Maraviroc QD - placebo: -0.853 (-1.217, -0.489). Maraviroc BID - placebo -1.021 (1.385, -0.658).	All-causality adverse events (AEs) were reported by between 85-92.3% of participants. Treatment related AEs were reported by approximately 41%, 49% and 42% of patients in the maraviroc QD, maraviroc BID and placebo treatment groups, respectively.Category C[4] infections and infestations: 4.3% of the maraviroc QD group, 4.7% of the maraviroc BID group, 1.7% of placebo patients. Deaths: 2 maraviroc QD, 4 maraviroc BID and 1 placebo. No death was considered treatment related. Permanent discontinuations due to study drug related AEs; 5 patients in the maraviroc QD group (for abdominal distension, aspartate transaminase increased, renal failure, rash, abdominal pain upper, and anaemia); 6 in the maraviroc BID treatment group (for transaminases increased, fatigue, abdominal pain upper, liver function test (LFT) abnormal, pyrexia, convulsion and rash generalised) and 3 in the placebo treatment group (for pyrexia, LFT abnormal and gingivitis).

[4] Defined according to the US Centres for Disease Control and Prevention (CDC) categories of HIV infection.

Table 3 Summary of Study A2001028

Investigator, Country, Year	Design/objectives	Participants	Immunogenicity results	Safety results
Multiple centres with multiple investigators in North America, Australia, Belgium, Canada, France, Germany, Italy, Netherlands, Poland, Spain, Sweden, Switzerland, United Kingdom, United States of America December 2004 to July 2007	A multicentre, double-blind, placebo-controlled trial, randomised 2:2:1 to treatment with maraviroc 300 mg once daily (QD) or maraviroc 300 mg twice daily (BID) in combination with optimised background therapy (OBT) versus matching placebo with OBT, designed to investigate the superiority of maraviroc against placebo. Primary objective: To assess whether maraviroc added to OBT provides an additional reduction in plasma HIV-1 RNA compared to OBT alone, as measured by the difference between each of the two maraviroc regimens versus the placebo regimen in the mean changes from baseline in plasma HIV-1 RNA at Week 48. If the 2-sided 97.5% confidence interval (CI) was completely to the left side and completely excludes zero, superiority of maraviroc over placebo was concluded. NB: in case of concomitant protease inhibitor use except tipranavir, and/or delavirdine use, the maraviroc dose was reduced from 300 mg to 150 mg.	CCR5 tropic HIV-1 infected patients ≥ 16 years of age with ≥ 6 months of prior treatment with at least 1 agent from 3 antiretroviral drug classes or documented multi-class resistance, with plasma VL ≥ 5,000 copies/mL. Screened: 1428 Randomised: 474 Treated: 464 Maraviroc QD: 182 Maraviroc BID: 191 Placebo: 91 Males 87%, over 80% White and the majority aged between 35 and 54 years.	Superiority was shown in the pre-defined terms. Adjusted mean changes from baseline in VL $\log_{10}$ copies/mL were: Maraviroc QD - 1.718 Maraviroc BID, - 1.865 Placebo – 0.757 The treatment differences (95% CI) were: For maraviroc QD - placebo: -0.961 (-1.379, -0.544) For maraviroc BID – placebo -1.109 (-1.523, -0.695).	About 92% of the maraviroc groups and 84% of the placebo group reported at least 1 AE. Treatment related AEs were reported by 60%, 55% and 50% of subjects in the maraviroc QD, maraviroc BID and placebo groups. The majority were Grade 1 or 2. Category C infections and infestations were reported by 16 of the maraviroc QD group, 8 in the maraviroc BID group and 9 in the placebo group. Deaths: 4 in the maraviroc QD group, 5 in the maraviroc BID group and 1 in the placebo group. No deaths considered treatment related. About 17% of patients in each group reported SAEs.Permanent discontinuations: 7 in the maraviroc QD group (for myalgia (2), muscular weakness, ALT and AST increased, peripheral oedema, anaemia and diarrhoea); 7 in the maraviroc BID group (for VL increased, hepatic failure, ALT and AST increased, syncope, bile duct cancer, orthostatic hypotension, and ALT, AST and GGT increased) and 3 in the placebo group (for cytolytic hepatitis, dizziness and hepatic enzyme increased).

Table 4 Summary of Study A4001029 – 48 Week Report

Investigator, Country, Year	Design/objectives	Participants	Efficacy results	Safety results
Multiple investigators at 72 centres in 9 countries: Australia, Belgium, Canada, Germany, Netherlands, Spain, Switzerland, the United Kingdom and the US. November 2004 to May 2006	A Phase IIb, multicenter, randomised, double-blind, placebo controlled trial of maraviroc in combination with optimised background therapy (OBT) versus OBT alone for the treatment of antiretroviral-experienced patients infected with non- CCR5 tropic HIV-1. Primary objective was to assess whether maraviroc added to OBT provided additional reduction in plasma VL compared to placebo plus OBT alone as measured by the difference in mean changes from baseline in plasma VL at Week 24. Secondary objective to make similar assessment at Week 48. Treatments were: Maraviroc 300 mg once daily (QD) plus OBT Maraviroc 300 mg twice daily (BID) plus OBT Placebo plus OBT. (Maraviroc 150 mg was substituted if the OBT contained ≥ 1 protease inhibitor and/or delavirdine. OBT included 3 to 6 approved antiretroviral agents (excluding low dose ritonavir)).	Patients ≥ 16 years with dual/mixed, CXCR4 or non-reportable/non-phenotypable HIV-1 infection with ≥ 3 months prior treatment with at least 1 agent from 3 of the 4 antiretroviral drug classes or documented resistance to members from 3 of 4 classes, a stable antiretroviral regimen for at least 4 weeks prior to randomisation and a plasma VL ≥ 5,000 copies/mL. Screened: 232, Randomised: 190 Treated: 186: Maraviroc QD: 63, Maraviroc BID: 61, Placebo: 62. Males 87%, White 64.5%, Black 29%, Asian 4.8% Age range 23-65 years	*48 week results* Discontinuations 114 (68%) The pre-defined criteria of superiority or non-inferiority of the 2 maraviroc regimens compared to placebo were not met. Only 9 participants had a valid tropism result at Week 48.	Treatment related adverse events were reported for 44.4% of the maraviroc QD group, 52.5% of the maraviroc BID group and 62.9% of the placebo group. Serious adverse events were reported for 15.9% of the maraviroc QD group, 16.4% of the maraviroc BID group and 17.7% of the placebo group. There were 2 deaths in the maraviroc QD group, 1 in the maraviroc BID group and 2 in the placebo group. Category C AIDS defining illnesses occurred in 8% of those treated with maraviroc QD, 7% of those treated with maraviroc BID and 3% of those on placebo. Discontinuations due to adverse events were reported for 2% of the maraviroc QD group, 3% of the maraviroc BID group and 8% of the placebo group.

Pharmacokinetics

Study A4001026 – Treatment naïve patients

Summary of results

Population pharmacokinetic (PK) parameters were estimated for use in exposure-response analyses and to explore the influence of covariates. Concentration versus time after dose data were compared with steady state results from Phase IIa study data and were found to be similar in distribution but with greater variability in Study A4001026 data. A significant effect of food in reducing the area under the plasma concentration-time curve (AUC)/average concentration by 11% was documented ($p < 0.001$).

An exploratory PK/pharmacodynamic (PD) analysis was undertaken on 48 Week data using Generalised Additive Models (GAM) to identify relationships between maraviroc 300 mg twice daily (BID) systemic exposure and clinical endpoints, in an effort to determine prognostic factors describing maraviroc effect on the safety and efficacy outcomes of virologic success, $CD4^+$ count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatine kinase (CK). Baseline $CD4^+$ count and baseline VL, baseline tropism, and exposure to maraviroc were found to be important prognostic factors of virologic success.

The results suggested that in the presence of zidovudine/lamivudine, at maraviroc average concentration 75 ng/mL, the probability of success would be 80% of maraviroc net effect. In Study A4001026, 13% of patients had maraviroc average concentrations less than 75 ng/mL. Minor prognostic factors were race, hemisphere, age, and clade.

Discussion

With respect to the population PK analysis, the sponsor's expert reviewer considered that the data demonstrating higher variability than found in previous studies could be expected from an outpatient study and a more heterogeneous population. The increased variability was considered likely to be the result of poor compliance and/or inaccurate dosing histories and/or a food effect. These differences, particularly in the absorption phase, were considered possibly the result of the (known) interaction of maraviroc with food. The Phase I/IIa data were mostly derived from dosing in the fasted state whereas in Study A4001026 maraviroc doses could be taken without regard to food. However, the expert considered the statistically significant food effect to be clinically insignificant.

With respect to the exploratory PK/PD analysis, in addition to baseline variables of $CD4^+$ count, VL and viral tropism, race, sex and age were found to influence the hepatic extraction ratio but were considered clinically insignificant by the expert. However, in an effort to maximise efficacy, it may be that taking such variables into consideration in treatment of individuals, rather than in determining clinical significance in populations, may contribute to improved response to treatment. Ultimately, the aim of undertaking studies of populations of HIV-1 infected patients should be to optimise the treatment of individual patients.

This PK/PD study potentially generates the hypothesis that attention to attaining a specific average concentration results in higher probability of success in treatment. As timing of drug administration with respect to food was determined in the population PK study to significantly influence drug levels, it is considered possible that maraviroc treatment may have been more successful if given in the fasted state. It may be that maraviroc efficacy could be enhanced by monitoring therapeutic drug levels.

It also appears that patients with high VLs were disproportionately represented amongst the treatment failures and for these patients, special attention to attaining adequate blood levels would appear wise.

Additionally and hypothetically, treatment naïve patients with very high viral counts may not be appropriate candidates for maraviroc treatment. The PK/PD analysis also determined that baseline $CD4^+$cell count and baseline viral count are potential determinants of treatment failure or success. As higher VLs and lower $CD4^+$cell counts with steep decline are associated with greater possibility that the patient harbours X4-using virus. This may have implication for the optimal time to initiate maraviroc therapy in treatment naïve patients. It is possible that high VLs result in competitive inhibition of maraviroc.

Pharmacodynamics

No specific studies were provided.

Efficacy

Study A4001026 – Treatment naïve patients

Summary of efficacy

The 96 Week report of this ongoing, Phase IIb/III, multi-national, multi-centre trial was submitted in support of registration of maraviroc 300 mg BID for treatment naïve patients infected with CCR5 tropic HIV-1. Maraviroc, 300 mg once daily (QD) and maraviroc 300 mg BID were evaluated in comparison to efavirenz 600 mg QD. Each was taken without food restriction in combination with zidovudine/lamivudine 300 mg/150 mg BID. The study included patients aged at least 16 years infected with CCR5-tropic HIV-1, and with a VL ≥ 2,000 copies/mL.

An interim analysis was performed when the first 205 patients reached Week 16. Based on failure to meet the non-inferiority criterion, the maraviroc QD arm was discontinued; patients responding to maraviroc were given the option to switch to open label (OL) maraviroc 300 mg BID. Participants were subsequently randomised 1:1 to maraviroc BID or efavirenz. A total of 695 patients were treated: 174 in the maraviroc QD group, 360 in the maraviroc BID group and 361 in the efavirenz group.

The primary objective was assessment of non-inferiority of maraviroc compared to efavirenz in terms of VL < 400 copies/mL and < 50 copies/mL at Week 48. The primary analysis was based on the 1-sided, 97.5% confidence interval (CI) with adjustment for the randomisation strata of screening VL and geographic region. Non-inferiority was concluded if the lower bound (LB) of the CI was above -10%. For the primary analysis, participants were stratified by geographic location (Northern or Southern Hemisphere) and screening VL (< 100,000 or ≥ 100,000 copies/mL). The Full Analysis Set (FAS) and the Per Protocol (PP) population results were analysed. Sensitivity analysis was performed using the Time to Loss of Virologic Response (TLOVR) algorithm.

The initially planned 1-sided significance level of 0.0125 (Bonferroni adjustment for multiple comparisons) was changed to the 1-sided 97.5% CI when the maraviroc QD group was discontinued.

Non-inferiority for VL < 400 copies/mL was demonstrated using the FAS; the LB of the 1-sided 97.5% CI was -9.5. However, non-inferiority was not demonstrated for VL < 400 copies/mL in the PP analysis, nor for VL < 50 copies/mL using either the FAS or PP analyses.

Virologic failure based on VL < 400 copies/mL was more commonly reported for non-responders in the maraviroc BID group than the efavirenz group: 27% versus 5.3%. Similarly for VL < 50 copies/mL the proportions were 32.0% versus 8.8%. However, the mean increase from baseline in $CD4^+$cell count throughout the 48 Weeks was consistently greater in the maraviroc group than in the efavirenz group; the difference between the maraviroc and efavirenz groups was 26.3 cells/µL (95% CI 7.0, 45.6).

Subgroup analysis by screening VL demonstrated a smaller response for maraviroc treated patients compared to the efavirenz group in terms of VL < 400 copies/mL and < 50 copies/mL in the stratum with ≥ 100,000 copies/mL at screening, as summarised in Tables 5 and 6, below. While subgroup analysis results are considered observational, it appears possible that patients with high VL at screening adversely influenced the overall result.

Table 5. Percentages with VL < 400 copies/mL at Week 48, by VL at screening

Viral Load at Screening	Maraviroc 300 mg BID % (n/N)	Efavirenz 600 mg QD % (n/N)
Total Population	70.6% (254/360)	73.1% (264/361)
<100,000 copies/mL	73.5% (150/204)	73.5% (155/211)
≥100,000 copies/mL	66.7% (104/156)	72.7% (109/150)

N= number of subjects in the treatment group in the indicated population
n = number of subjects with a post baseline observation used to calculate the percentage

Table 6. Percentages with VL <50 copies/mL at Week 48, by VL at Screening

Viral Load at Screening	Maraviroc 300 mg BID % (n/N)	Efavirenz 600 mg QD % (n/N)
Total Population	65.3% (235/360)	69.3% (250/361)
<100,000 copies/mL	69.6% (142/204)	71.6% (151/211)
≥100,000 copies/mL	59.6% (93/156)	66.0% (99/150)

N= number of subjects in the treatment group in the indicated population
n = number of subjects with a post baseline observation used to calculate the percentage

The percentage of participants in the QD group with VL < 400 and < 50 copies/mL at Week 96 was 52.9% and 48.3%, respectively, while the results for those treated with OL maraviroc 300 mg BID were 70.8% and 64.6%, respectively.

Study A4001026 utilised the original Trofile assay (OTA), the only available tropism test at the time. Shortly after completion of the study, the Enhanced Sensitivity Trofile Assay (ESTA) was released for clinical use, based on data demonstrating increased sensitivity for the detection of CXCR4 tropic virus. A post hoc analysis using the primary analysis statistical approach was undertaken to determine whether the use of ESTA would have excluded more patients unlikely to respond to maraviroc. Based on ESTA, the proportions re-classified as dual/mixed (D/M) tropic or CXCR4 tropic were 48 (13.3%) and 58 (16.1%) in the maraviroc 300 mg BID and efavirenz arms, respectively.

Re-analysis of the outcome of viral count < 400 copies/mL confirmed the original finding of non-inferiority using the FAS, supported by the PP analysis. For viral count < 50 copies/mL the re-analysis adjusted for randomisation strata of screening VL and geographic region resulted in a LB of the 97.5% CI above -10%, supported by the PP analysis. However, the 48 Week FAS and PP sensitivity analysis using the TLOVR algorithm failed to support the finding. Results for 96 Weeks also resulted in lower CI bounds of less than -10%.

The initial inequality in proportions of participants discontinuing due to lack of efficacy remained after the ESTA analysis. On re-analysis, discontinuations due to lack of efficacy were recorded for 9.3% of the maraviroc BID groups, compared with 4% of the efavirenz group.

Discussion of efficacy

The EU Guideline on the *Clinical Development of Medicinal Products for the Treatment of HIV infection*[5] recommends that the proportion achieving and maintaining plasma HIV ribonucleic acid (RNA) < 50 copies/mL is the preferred primary efficacy endpoint for studies in treatment naïve populations. The EU Guideline on *Points to Consider on Switching Between Superiority and Non-inferiority*[6] states that in a non-inferiority trial, the FAS and the PP analyses are considered to have equal importance and their use should lead to similar conclusions for a robust interpretation. This Guideline also states that when a one sided CI is chosen, 97.5% CI is considered appropriate.

The initially planned 1-sided significance level of 0.0125 (Bonferroni adjustment for multiple comparisons) was changed to a 1-sided 97.5% CI when the maraviroc QD group was discontinued, which is a matter requiring justification. It is also considered that further adjustment for multiplicity should have factored in the repeated testing related to the interim analysis.

Study A4001026 demonstrated non-inferiority only for viral count < 400 copies/mL and only for the FAS, and failed to demonstrated non-inferiority based on viral count < 50 copies/mL according to the pre-planned statistical analytic plan.

The observational ESTA analysis resulted in a dropout rate of 13.3% for the maraviroc group and 16.1% of the efavirenz group, due to reassessment of tropism. The numbers with change of tropism between screening and baseline following re-analysis could not be located in the dossier. By its nature, the analysis had the potential to unbalance confounding factors and include bias.

The findings of the ESTA analysis in relationship to the primary objective supported non-inferiority based on VL < 400 copies/mL and < 50 copies/mL. However the findings were not uniformly supported by sensitivity analysis. In addition, the analysis used the 1-sided 97.5% CI without consideration of the possible multiplicity issue related to repeat testing.

The selection of a comparator arm was based on the preferred regimen for the treatment of established HIV infection in antiretroviral naïve patients at the time the study was designed (2003)[7] and is being judged accordingly; however, this is currently recommended as an alternative regimen in the US Department of Health and Human Services *Guidelines for use of antiretroviral agents in HIV-1-infected adults and adolescents* (Australian commentary).[8] The sponsor argued that the efavirenz response in this study was lower than that seen in other studies in which tenofovir and emtricitabine have been used as backbone, and that it is possible that the use of a more potent backbone such as tenofovir and emtricitabine would have led to an increased response rate in both treatment groups.

While it is possible that efficacy results would have been different using a different backbone regimen or if it had been possible to prospectively plan the study using ESTA to screen for non-CCR5 tropic virus, it is not considered appropriate to make a recommendation for registration based on possibilities.

[5] EMEA/CPMP/EWP/633/02, 20 November 2008; adopted in Australia.
[6] CPMP/EWP/482/99, 27 July 2000; adopted in Australia.
[7] The EACS Euroguidelines Group. European guidelines for the clinical management and treatment of HIV-infected adults in Europe. AIDS 2003:17;S3-S26.
[8] HHS Guidelines for the use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents with Australian commentary. Available at <http://ashm.org.au/projects/arvguidelines/Default.asp?PublicationID=4>

Statistical issues

The TGA sought expert statistical advice regarding the importance of multiplicity issues in this study. The expert concluded that:

For the original ITT (and PP) groups, statistical non-inferiority has not been proven according to standard, commonly-used and accepted criteria for statistical non-inferiority.

Of more current clinical relevance are the results for the subgroup defined according to the ESTA. Such post hoc, subgroup analyses are notoriously difficult to assess. From a purely statistical viewpoint, the main difficulty is the problem of multiplicity. That is, multiplicity is a concern for the post hoc subgroup analysis defined according to the ESTA.

Summary of virology

At the time of treatment failure at the Week 48 assessment, 27/43 (62.8%) of the maraviroc BID group and 3/15 (20%) of the efavirenz group had virus with genotypic evidence of resistance to lamivudine. In addition, 6/43 (14.0%) in the maraviroc BID treatment group had virus with zidovudine resistance as evidenced by the presence at discontinuation of one or more thymidine analogue-associated mutations (TAMs). None of the 15 participants who failed efavirenz had virus with TAMs at failure. The 48 Week assessment of discontinuations and the Week 96 findings for treatment failure and discontinuations demonstrated a similar pattern.

With respect to the maraviroc QD treated participants who either discontinued or were changed to OL maraviroc BID, 27 participants overall and 16 who entered OL treatment had treatment failure due to insufficient clinical response. At the time of treatment failure, 20/27 individuals (74.1%) overall and 13/16 (81.3%) who entered OL treatment had virus with genotypic evidence of drug resistance to lamivudine; three of whom had virus with zidovudine resistance.

A total of 77 participants in all, and 33 who entered OL treatment, discontinued study treatment. At time of discontinuation, 31/77 (40.3%) overall and 19/33 (57.6%) who entered OL treatment had virus with genotypic evidence of drug resistance to lamivudine; three of whom had virus with zidovudine resistance, as evidenced by the presence at discontinuation of 1 or more TAMs.

Sequences of the V3 loops[9] were obtained for 6 participants whose CCR5 tropic virus showed reduced susceptibility to maraviroc in Study A4001026. Changes in the V3 loop sequence were identified in clones from 5/6 participants. Consistent with similar studies in treatment experienced participants, no signature mutations of maraviroc resistance were identified, suggesting that there are multiple pathways to maraviroc resistance *in vivo*.

In the 6 week period between screening and baseline, approximately 3–4% of participants in the maraviroc BID and efavirenz groups switched from CCR5 tropic to D/M tropic. At the Week 48 assessment, 10/32 participants in the maraviroc BID group with treatment failure and available results switched to CXCR4 or D/M tropism; at Week 96, 12/34 in the maraviroc BID group changed tropism. None of the 15 failures in the efavirenz group did so.

At Week 48, 12/75 (16%) patients in the maraviroc group who discontinued the study changed tropism from CCR5 to CXCR4 or D/M tropic. At Week 96, 14/106 (13%) of patients in the maraviroc BID group who discontinued from the study changed viral tropism to CXCR4 or D/M, while at neither time point did any of the participants in the efavirenz group do so.

[9] part or region of the HIV virus that allows it to infect human immune cells by binding to a cytokine receptor such as CCR5 or CXCR4.

The median time to treatment failure was shorter for participants who were CCR5 tropic at baseline and who remained CCR5 tropic or who were not reportable/non-phenotypable (NR/NP) tropic at treatment failure in the maraviroc compared to the efavirenz group.

With respect to the maraviroc QD participants who either discontinued or were changed to OL maraviroc BID, five participants with D/M tropism at baseline had D/M tropism at the time of treatment failure. Four participants with CCR5 tropism at baseline had D/M tropism at the time of treatment failure. Seven of 9 participants who failed with CCR5 tropic virus and 9/9 who failed with D/M tropic virus had evidence of zidovudine/lamivudine resistance.

Discussion of virology

Based on the subgroup analyses it appears that maraviroc treatment failure may increase the risk of selection of non-CCR5 tropic virus. Non-CCR5 tropic, syncytium forming virus has been shown to be associated with a faster rate of disease progression.

Based on subgroup analyses, it appears possible that the patients who failed treatment with maraviroc were at greater risk than those treated with efavirenz of developing resistance to background therapy of lamivudine and zidovudine. Failure to achieve VL < 50 copies/mL may have predisposed to development of viral resistance.

With respect to the maraviroc QD group, efficacy results for the OL group were biased by inclusion of participants who were known to be responding to treatment and who voluntarily changed to OL treatment. It is presumed that the participants who discontinued maraviroc treatment were treated with other antiretroviral therapy and it appears that there was a continuing drop in the proportions with VL < 400 copies/mL or < 50 copies/mL in this group. It could be hypothesised that this represents an indication that disease progression had been adversely affected by the change of viral tropism.

Also in relation to the QD and OL groups, it appeared that early treatment failure with either CCR5 or D/M tropisms may be associated with an increased tendency towards development of viral resistance to the background agents, in particular lamivudine.

Studies A4001027 and A4001028 – Treatment experienced patients

Summary of efficacy

These identically designed, multicentre, randomised, double-blind, placebo-controlled trials compared maraviroc 300 mg QD or maraviroc 300 mg BID in combination with optimised background therapy (OBT) versus OBT plus matching placebo for the treatment of antiretroviral-experienced patients infected with CCR5 tropic HIV-1.

The studies included patients aged ≥ 16 years with plasma VL ≥ 5,000 copies/mL with ≥ 6 months of prior treatment with at least 1 agent from 3 of the 4 antiretroviral drug classes or documented resistance to members from 3 of 4 classes and a stable antiretroviral regimen for at least 4 weeks prior to randomisation. Infection with non-CCR5 tropic virus was an exclusion criterion.

The primary efficacy objective was to test superiority of the two maraviroc regimens versus placebo in terms of the difference in the mean change from baseline in plasma HIV RNA at 48 Weeks. The 2-sided 97.5% CI for the difference was adjusted for multiplicity. Superiority of maraviroc versus placebo was concluded if the upper CI limit for the difference in treatment mean was completely to the left side excluding zero. An interim analysis of the primary objective was undertaken at 24 Weeks at which time the sponsor was unblinded.

In both studies for both maraviroc dosing regimens superiority was demonstrated compared with placebo. In Study A4001027 the decrease in HIV-1 RNA from baseline to Week 48 was -1.66 $\log_{10}$ copies/mL for maraviroc QD and -1.82 $\log_{10}$ copies/mL for

maraviroc BID, versus -0.80 log_{10} copies/mL for placebo. The treatment difference from placebo was -0.85 log_{10} copies/mL (97.5% CI -1.22, -0.49) for maraviroc QD and -1.02 log_{10} copies/mL (97.5% CI -1.39, -0.66) for maraviroc BID. In Study A4001028 the decreases in HIV-1 RNA for maraviroc QD, BID and placebo were -1.72 log_{10} copies/mL, -1.87 log_{10} copies/mL and -0.76 log_{10} copies/mL, respectively. The treatment difference was -0.96 log_{10} copies/mL (97.5% CI -1.38, -0.54) for maraviroc QD and -1.11 log_{10} copies/mL (97.5% CI -1.52, -0.70) for maraviroc BID.

There were more discontinuations due to lack of efficacy in the placebo arm (53%) than in either maraviroc arm (20-25%). The proportion of patients with VL < 50 copies/mL at Week 48 was 40.7% in the maraviroc QD group, 46.6% in the BID treatment group and 15.4% in the placebo group. In both studies, there was a greater mean increase in $CD4^+$ and $CD8^+$ cell counts from baseline in both maraviroc treatment groups compared with placebo.

Discussion of efficacy

With regard to the primary objective, superiority was demonstrated for both maraviroc regimens compared to placebo. This was achieved despite use of the OTA in determining suitability for inclusion in the study. However, it is considered unusual to undertaken an interim analysis based on the criteria for the primary analysis and to unblind any participating, interested party at that the time.

Although the significance level was adjusted for multiplicity related to comparison of two dosage regimens with placebo, the issue of whether repeated testing was considered in relation to the interim analysis was not addressed.

Summary of virology

The majority of patients had either no change in their susceptibility scores (genotypic susceptibility score (GSS), phenotypic susceptibility score (PSS) and overall susceptibility score (OSS)) or had a loss of susceptibility to one drug, with very few patients having an increase; the small shift being consistent with the fact that most patients had GSS, PSS and OSS values of ≤ 2 at screening. Subpopulation analysis showed an increase in response in terms of VL < 50 copies/mL with increase in GSS and OSS.

In Studies A4001027 and A4001028, 20/56 (36%) participants who experienced protocol defined treatment failure with CCR5 tropic virus to Week 48 were found to have reduced susceptibility to maraviroc, with reduced maximum percentage inhibition (MPI). Amino acid changes in the V3 loop of envelope clones were identified in viruses from patients which showed a plateau in MPI after treatment with maraviroc. However, these changes were different between patients, reflecting the heterogeneity in envelope glycoprotein gp160 sequence; signature mutations of maraviroc resistance were not identified.

A change in viral tropism between screening and baseline was reported for 7% of participants in Study A4001027 and 8% in Study A4001028, all changes were from CCR5 to D/M. In each of the studies, most of the participants who responded to treatment had no tropism assignment at Week 48, mainly due either to having VL < 500 copies/mL or having discontinued.

In Study A4001027, of the 252 patients with a CCR5 tropism at baseline who experienced treatment failure, 82 (32.5%) had a change in tropism result to CXCR4 or D/M at the time of treatment failure. All but 6 of these patients were in the maraviroc treatment arms.

In Study A4001028, of the 107 participants with a CCR5 tropism result at baseline, and who experienced treatment failure, 25 (23%) had a change in tropism result to CXCR4 or D/M at the time of treatment failure; all but 3 of these participants were in the maraviroc treatment groups.

Discussion of virology

It was noted that the significance or otherwise of change of tropism appears to be dependent on the model used for analysis based on the way of handling missing values. It may be that the Last Observation Carried Forward (LOCF) model may be more meaningful as there were otherwise large numbers of missing values reported at Week 48. Using the LOCF model, the CIs for the difference between maraviroc and placebo at Week 48 and at the time of treatment failure both suggest a significant difference between maraviroc and placebo in the proportions undergoing change of tropism, which is of potential concern considering the possibility of more rapid disease progression in the presence of CXCR4-using virus.

Study A4001029 – Non-tropic CCR5

Summary

Study A4001029 was a multicenter, double-blind, randomised, placebo-controlled Phase IIb study of heavily treatment experienced patients infected with non-CCR5 tropic (dual tropic, CXCR4 tropic or non phenotypable) HIV-1, assessed using the Trofile assay. The primary objective was to determine whether maraviroc 300 mg QD or BID added to OBT provided an additional reduction from baseline in plasma VL compared to OBT alone at Week 24 (results not included in the submitted report). A similar analysis at Week 48 was a secondary objective.

The study included patients aged at least 16 years, infected with non-CCR5 tropic HIV-1, with ≥ 3 months of prior treatment with at least 1 agent from 3 of the 4 antiretroviral drug classes or documented resistance to members from 3 of 4 classes, a stable antiretroviral regimen for at least 4 weeks prior to randomisation and a plasma VL ≥ 5,000 copies/mL.

Sixty-three patients were treated in the maraviroc QD group, 61 in the maraviroc BID group and 62 in the placebo group. The proportions discontinued by Week 48 were 76% of the maraviroc QD group, 59% of the maraviroc BID group and 71% of the placebo group.

Approximately 87% of the study population was male and the majority were aged between 35 and 54 years. Approximately two thirds were White and one third was Black. The commonest reason for exclusion from the PP analysis was presence of CCR5 virus only at baseline, which was reported for 6.3% of the maraviroc QD group, 9.8% of the maraviroc BID group and 11.3% of the placebo group.

Neither maraviroc dose regimen demonstrated superiority or non-inferiority to placebo. The percentage discontinuing for lack of efficacy was 64% for the maraviroc QD group and 44% for both the maraviroc BID and placebo groups.

Category C AIDS-defining illnesses were reported for 8% of patients receiving maraviroc QD, 7% receiving maraviroc BID, and 3% of participants receiving placebo.

Discussion

The numbers in the study were small and the proportions discontinuing were considerable. Of the patients with D/M tropism at baseline and with a result available at the time of treatment failure, 26/68 (38%) patients treated with maraviroc had a CXCR4 tropism result at failure, compared with 3/27 (11%) patients in the placebo group, consistent with possible selective suppression by maraviroc of CCR5 tropic virus strains in these patients. It was not clear to the evaluator whether those in the study with CXCR4 had a more rapid clinical deterioration thereafter or were more resistant to further treatment. However, the use of maraviroc in treatment of non-CCR5 tropic virus is not proposed.

Safety

Study A4001026 – Treatment naïve patients

Summary of safety

The total exposure in patient-years was 506 years for maraviroc and 507.9 years for efavirenz. All-causality adverse events (AEs) were reported by similar proportions of the maraviroc BID and efavirenz groups. However, treatment related AEs and discontinuations due to treatment related AEs were more common in the efavirenz group than in the maraviroc BID group. Adverse events leading to permanent discontinuation were considered treatment related by the investigator for 15 (4.2%) in the maraviroc group and 47 (13.0%) in the efavirenz group. The most common reasons for discontinuation were related to increased transaminases, nausea and pregnancy in the maraviroc BID group; and rash, pregnancy, tuberculosis, dizziness and nausea in the efavirenz group.

There appeared no evidence relating maraviroc BID to an excess of deaths, Category C infection, serious AEs, malignancy, hypotension, infection, hepatobiliary disorder or QTcF prolongation[10] in comparison to efavirenz. No new or unexpected safety signal was reported.

Discussion of safety

While efficacy is an issue, it appeared that maraviroc BID has an advantage which demonstrated a better safety profile than efavirenz with respect to safety, as shown in this study to this time point. There was benefit in favour of maraviroc compared to efavirenz with respect to discontinuations due to AEs and with respect to lipid parameters. There was no category of events in which maraviroc predominated compared to efavirenz. In particular, in areas of special interest, there were no more malignancies reported, no evidence of an increased incidence of Category C events and AIDS, and no excess of thyroid or muscle related AEs.

With respect to determining the clinical significance of a change in tropism, the timing of the event is of importance as there is likely to be a lag time between change of tropism and the onset of accelerated disease progress or AEs related to progression to AIDS. Submission to the TGA of the results of the ongoing follow-up is considered a requirement should maraviroc be registered for use in treatment naïve patients.

With respect to QTcF interval, details of the uniformity or otherwise of collection, reading and interpretation of the electrocardiograms (ECGs) could not be located in the submission dossier. Increases in QTcF of as little as 30 msec or less may be clinically relevant.[11] Based on Committee for Proprietary Medicinal Products (CPMP) recommendations,[12] 16% of patients in the maraviroc group had maximum increases in the range at least potentially of concern, versus 17% of the efavirenz group. The fact that one group did not predominate in incidence is not totally reassuring.

[10] The QT interval is the portion of an electrocardiogram between the onset of the Q wave and the end of the T wave, representing the total time for ventricular depolarization and repolarization. QTc is the QT interval adjusted for heart rate. QTc calculated using a correction factor developed by Louis Friderica is identified as QTcF. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias such as torsade de pointes and sudden death.

[11] J. Morganroth. Focus on issues in measuring and interpreting changes in the QTc interval duration. *Eur Heart J Supplements* 2001;3(Supplement K):K105–K111, available at: <http://eurheartjsupp.oxfordjournals.org/content/3/suppl_K/K105.full.pdf>

[12] CPMP Guideline on *Points to consider: The assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products*. CPMP/986/96. December 1997.

With respect to maraviroc QD: despite demonstrated superiority of efficacy of maraviroc 300 mg QD with OBT in treatment experience patients, albeit with a different primary outcome, its use in treatment naïve patients was found to be inferior such that discontinuation of that treatment was advised by the Data Safety Monitoring Board. While the QD dose is not the subject of the application, the apparent efficacy failure is of concern as it points to the possibility that the treatment naïve patients offer challenges in treatment not so evident in the treatment experienced population.

Studies A4001027 and A4001028 – Treatment experienced patients

Summary of safety

The numbers included in the safety analysis were: maraviroc QD (414), maraviroc BID (426), placebo (209), and in-study on OL maraviroc BID (117 participants). Total exposure in patient years was 300–308.8 for the blinded maraviroc arms and 110.7 for placebo.

All causality AEs were reported by similar proportions of the maraviroc and placebo groups, not taking into account the different lengths of exposure. The incidence of treatment related AEs was 49.5% for maraviroc QD, 51.4% for maraviroc BID, and 45.0% for the placebo group. The most common of these were nausea, diarrhoea, fatigue, headache and dizziness. Rash, constipation, dyspepsia and cough occurred at ≥ 2% and at a higher incidence in the maraviroc BID group than the placebo group.

Serious AEs were reported by 76/414 (18.4%) on maraviroc QD, 88/426 (20.7%) on maraviroc BID and 38/209 (18.2%) on placebo. The most common serious AEs were vomiting and pneumonia. Two deaths were considered treatment related, both reported in maraviroc treated patients: due to large cell lymphoma and cholangiocarcinoma with multiple metastases, respectively.

Permanent discontinuations because of all-causality AEs were reported by 20 (4.8%) receiving maraviroc QD, 19 (4.5%) receiving maraviroc BID and 11 (5.3%) receiving placebo.

More liver related AEs were reported by participants in the maraviroc groups. The approved Celsentri PI in the *Precautions* section is considered adequate to cover this event.

There appeared no evidence relating maraviroc BID to an excess of deaths, Category C infection, serious AEs, malignancy, hypotension, infection or QTcF prolongation in comparison to placebo. No new or unexpected safety signal was reported.

Discussion of safety

Based on Week 48 results there appears to be no change in the safety profile of maraviroc in treatment of treatment experienced patients. A brief mention of Week 96 results made by the sponsor's clinical expert leads to the conclusion that there may possibly be further safety information available to the sponsor. If so, it is recommended that the data is submitted to the TGA.

List of questions

The TGA provided the sponsor a copy of the CER, along with an invitation to provide a response to matters raised therein.

First round clinical summary and conclusions

Benefit risk assessment

Benefits

Benefits for treatment experienced patients

Superior efficacy of maraviroc 300 mg BID compared to placebo has been established in Studies A4001027 and A4001028. The Week 48 safety assessment of maraviroc use in treatment experienced patient has revealed no new or unexpected safety signals.

Benefits for treatment naïve patients

Maraviroc 300 mg BID demonstrated a better safety profile than efavirenz with respect to discontinuations due to AEs and with respect to lipid profile (cholesterol, low density lipoprotein (LDL) and triglycerides).

Risks

Risks for treatment experienced patients

Selection pressure resulting in transition to CXCR4-using HIV-1 infection is possible. CXCR4 tropic virus has been associated with more rapid advancement of disease. The safety follow-up period of 48 months is relatively short. Rare AEs may remain to be identified.

Risks for treatment naïve patients

Non-inferiority with respect to efficacy is not considered to have been unarguably demonstrated.

In patients with viral failure there appeared to be an increased risk of development of resistance to the two agents used in the OBT, in particular to lamivudine and in particular in the presence of CXCR5-using virus.

At the time of treatment failure, for those patients with available results, only participants in the maraviroc group were documented to switch from CCR5 to CXCR4 or D/M virus. It is considered of concern that in the relatively early stages of illness, a patient may be put at greater risk of a change in tropism resulting in infection with a more virulent virus potentially leading to more rapid disease progression.

Patients with inadequate maraviroc blood levels have been shown to be at greater risk of treatment failure and hence of development of resistance and change of tropism, which is of concern in the absence of a requirement for therapeutic blood level monitoring.

Little detail regarding the ESTA could be located in the submission dossier. It appears that the commercially available assay requires a VL of at least 1,000 copies/mL, which may limit the early detection of X4-using virus. The length of time required for assay turnaround is considered a practical consideration as change of tropism in a short period of a few weeks has been shown to occur. In addition, the cost of the assay is a practical consideration to be determined.

Balance

With respect to treatment experienced patients and the already approved *Indication*, the risk-benefit profile is considered to remain positive.

For treatment naïve patients, the risk-benefit balance is considered to lie on the side of risk.

First round recommendation

Extension of the *Indication* to include treatment naïve patients is not recommended.

Continued registration of maraviroc 300 mg BID for use in treatment experienced population of HIV-1 CCR5 tropic viral infection is recommended.

It is recommended that issues raised with respect to the draft PI are addressed. Details of these are beyond the scope of this AusPAR.

Sponsor's response to the clinical evaluation report

The sponsor provided responses to address the clinical evaluator's concerns with respect to the robustness of the efficacy data and the potential risks associated with viral resistance and change in tropism. The response included supplementary data from the 5 year Study A44001026 in treatment naïve patients. A summary of the clinical evaluator's evaluation of the sponsor's responses and supplementary data is below, under *Supplementary Clinical Evaluation Report*.

The sponsor also provided revised PI and CMI documents that addressed the clinical evaluator's recommendations. Details of these are beyond the scope of this AusPAR.

Supplementary clinical evaluation report

A supplementary CER was prepared to take into account the sponsor's comments on issues raised in the initial CER and to evaluate the supplementary clinical data provided, which included an efficacy analysis at 240 Weeks from the recently available full report for the 5 year Study A4001025 in treatment naïve patients.

Statistical issues – Treatment naïve patients

The clinical evaluator was concerned that multiplicity was not taken into consideration in the statistical analysis for Study A4001026.

The sponsor's summary response stated that *'Multiplicity is not considered an issue with respect to the statistical analyses (interim analysis, FAS and PP data sets, secondary analyses at Week 96, Trofile and ESTA analyses and sensitivity analyses)'.*

TGA referred the sponsor's full response to an expert statistician for evaluation. The expert concluded that:

- The reanalysis, based on the more sensitive ESTA, is subject to multiplicity (by definition).
- It is difficult to be precise about the extent/level of concern generated by multiplicity. Nevertheless, the methodological problems generated by multiplicity, in this particular instance, are at the low level of concern. For this particular unusual instance (where a subgroup analysis is based on a more sensitive assay), multiplicity is not such a major concern that it, on its own, would be a reason for rejection of the application.
- Other statisticians might reasonably take a harder line and argue that post hoc subgroup analyses can only ever be hypothesis generating.
- The available statistical evidence suggests that maraviroc is either non-inferior to efavirenz or narrowly inferior to efavirenz.
- This is as far as the statistical analysis can take us. As the sponsor's response suggests, these statistical results would need to be considered in conjunction with background clinical knowledge (for example, information on resistance to maraviroc and resistance to backbone nucleoside/nucleotide reverse transcriptase inhibitor (NRTI)).

Efficacy - Treatment naïve patients– 240 Week data

Sponsor's response

Based on the ESTA analysis, at Week 240, VL < 50 copies/mL was observed for 158/311 patients (50.8%) in the maraviroc group, versus 139/303 (45.9%) in the efavirenz group. Based on the OTA analysis, the results were: maraviroc BID (176/360, 48.9%) and efavirenz QD (165/361, 45.1%). See Table 7 and Figure 1, below.

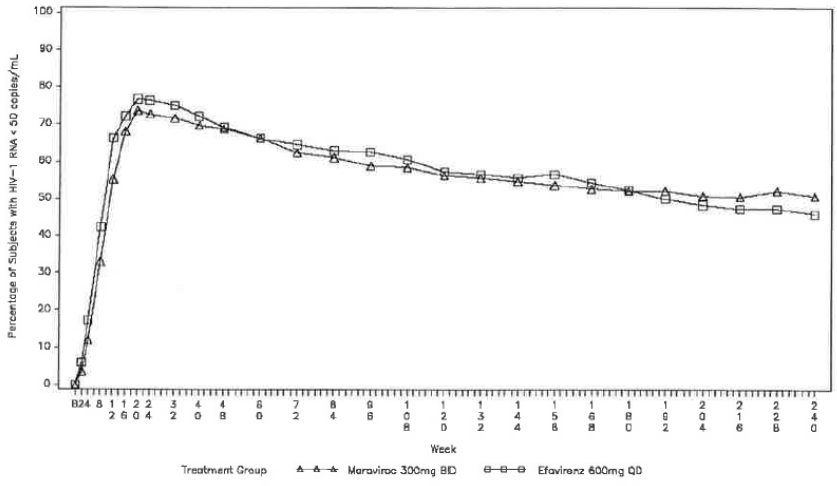
At Week 240, the mean changes from baseline in CD4+ cell count by visit (LOCF) for the maraviroc BID group was 292.9 cells/µL, versus 270.6 cells/µL for the efavirenz QD group (Table 8 and Figure 2, below).

Table 7. Patients with VL < 50 copies/mL at Weeks 48, 96 and 240 in Study A4001026

Number (%) of Subjects	MVC 300 mg BID	EFV 600 mg QD
ESTA R5 Subjects	**N=311**	**N=303**
Week 48	214 (68.8)	210 (69.3)
Week 96	184 (59.2)	189 (62.4)
Week 240	158 (50.8)	139 (45.9)
All Subjects	**N=360**	**N=361**
Week 48	236 (65.6)	253 (70.1)
Week 96	206 (57.2)	225 (62.3)
Week 240	176 (48.9)	165 (45.7)

Missing data = failure.
N Number of subjects in the treatment group in the indicated population used to calculate the percentage.
Abbreviations: BID = twice daily; EFV = efavirenz; ESTA = enhanced sensitivity Trofile assay; MVC = maraviroc; NA = not applicable; QD = once daily

Figure 1. Percentage of participants with VL < 50 copies/mL - ESTA R5 participants Study A4001026



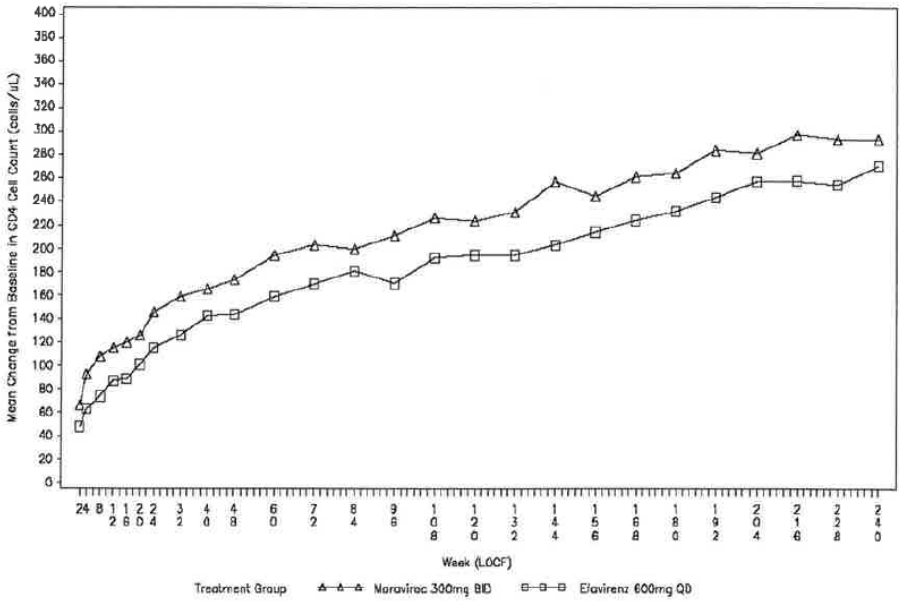
Discontinuations and failures are included at all time points
Missing data = failure.
Abbreviations: B = Baseline visit; ESTA = enhanced sensitivity Trofile assay; BID = twice daily; HIV = human immunodeficiency virus; QD = once daily; RNA = ribonucleic acid.

Table 8. Summary of change from baseline in CD4+ cell count (cells/µL) - ESTA R5 participants. Study A4001026 (LOCF)

Number of Subjects	MVC 300 mg BID N=311	EFV 600 mg QD N=303
Week 24		
n	303	291
Mean (SD)	145.4 (117.4)	115.30 (114.1)
Week 48		
n	303	291
Mean (SD)	173.3 (132.0)	143.59 (123.5)
Week 96		
n	303	291
Mean (SD)	211.5 (151.9)	170.71 (149.5)
Week 240		
n	303	291
Mean (SD)	292.9 (229.9)	270.58 (230.3)

The baseline value used in the calculation of change from baseline was the average of the pre-dose measurements collected at the screening and baseline visits.
N The number of subjects in the treatment group in the indicated population
n The number of subjects contributing to the summary statistics
Abbreviations: BID = twice daily; CD = cluster of differentiation; ESTA = enhanced sensitivity Trofile assay; LOCF = last observation carried forward; MVC = maraviroc; QD = once daily; SD = standard deviation.

Figure 2. Mean change from baseline in CD4+ cell count (cells/µL) LOCF) - ESTA R5 Participants. Study A4001026



The baseline value used in the calculation of change from baseline was the average of the pre-dose measurements collected at the screening and baseline visits.
Abbreviations: B = Baseline visit; BID = twice daily; ESTA = enhanced sensitivity Trofile assay; LOCF = last observation carried forward; QD = once daily.

Evaluator's comment

Based on the limited information supplied, efficacy in terms of VL < 50 copies/mL and CD4+ cell count appears well maintained for those who responded initially. The number and nature of study drop-outs and the viral tropism results for patients who failed treatment or developed AIDS related illness and died are of interest, along with general safety information.

Clinical pharmacology

Sponsor's response

- Major predictors for lack of response to maraviroc treatment in A4001026 were having the tropism result change from R5 tropic at screening to D/M at baseline, and low maraviroc average concentration or minimum concentration (Cmin).
- Since Study A4001026 was an outpatient study and maraviroc concentrations were measured after patients reported dosing there is confounding of low concentrations with poor adherence.
- Phase I/IIa data shows that below the limit of quantification (BLQ) observations with 300 mg BID dosing are highly unlikely, whether given with or without food within 24 h of a reported dose; therefore BLQ values for maraviroc can be used as a measure of poor adherence.
- After taking BLQ and the ESTA population into consideration, average concentration is not as important for predicted efficacy at the dose studied, compared to the GAM analysis with the original Trofile population
- Exposure-response curve flattened at the lower exposures in the new analysis (ESTA population) where participants with BLQ values (evidence of poor adherence) were censored.

Although food, gender, race and age have an effect on maraviroc PK, their influence on efficacy should be minimal given the lack of a strong exposure-response curve observed after adjusting for participants with poor adherence.

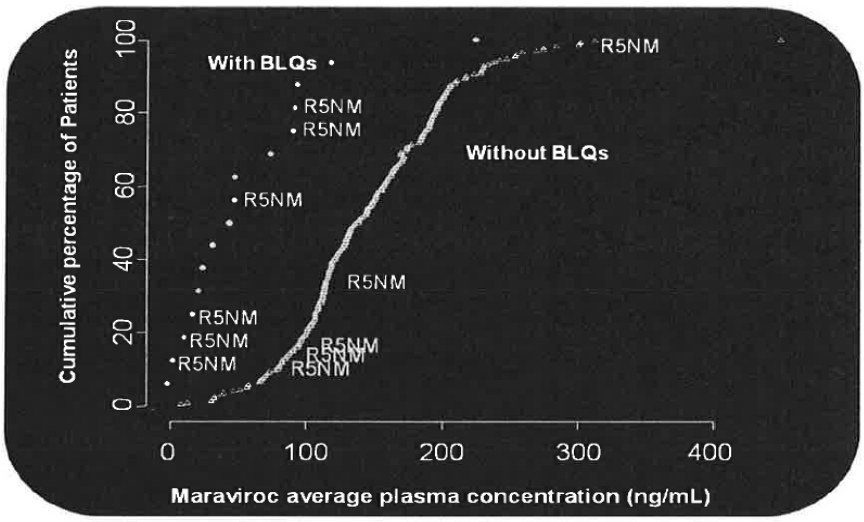
Evaluator's comment

The arguments above are largely accepted. It is reasonable that patients who are non-R5 tropic will not respond and neither will patients who are not taking medication and are, hence, BLQ.

The sponsor submitted concentration-time data for Study A4001007 demonstrating that in HIV-1 patients with maraviroc doses of 50 mg BID, concentrations were measurable to at least 48 h after the last dose in 7 of the 8 participants. For those dosed with 100 mg BID, all had measurable concentrations and the majority had measureable concentrations to 72 h. For those taking 300 mg BID, all participants had measurable concentrations to 72 h and 5 of 8 were above BLQ at 120 h after the last dose. These data are taken to suggest that patients with levels BLQ are likely to have been non-compliant.

Maraviroc levels BLQ were generally associated with treatment failure in the presence of maraviroc sensitive virus and without NRTI mutations. This is considered likely to be because patients who are non-compliant with one medication are also likely to be non-compliant with other medications. The figure does suggest that patients with quantifiable low average concentrations are more likely to develop lamivudine resistance; however, this exploratory finding is hypothesis generating and not definitive. Figure 3, below, illustrates the likely association of failure of treatment with CCR5 tropic virus and no mutation in the presence of maraviroc BLQ or low quantifiable average concentration.

Figure 3. Lack of Resistance (R5NM = CCR5 tropic with no mutations) at failure in Study A4001026 Based on average concentration and whether participant had maraviroc BLQ values



Abbreviations: BLQ = below limit of quantification; Cavg = average concentration; CCR5 = chemokine (C-C motif) receptor 5; MVC = maraviroc

It is noted that three quarters of patients in the lowest Cmin quartile had not been recorded as having values BLQ. This may have been because of timing of sampling, or the knowledge of impending medical assessment leading to increased compliance in the days leading up to the assessment; however, it is possible that the patients in the lowest quartile have some genetically determined reason for the low level and would benefit from an increase in dose. The sponsor argues that increase in dose based on Cmin may result in unacceptable increases in Cmax which might in turn result in postural hypotension. If this were to be the case, then increased dose frequency may be required rather than increased dose, *albeit* this is a less practical dose regimen.

Virology

Sponsor's response

In patients who developed resistance on the trial, the mutation that developed most commonly was that for lamivudine (M184V mutation). The clinical significance of this mutation has been debated for years as this mutation leads to a less fit virus which is less pathogenic, and most treatment guidelines suggest maintaining selection pressure for this mutation once it has been identified.

Among patients who discontinued due to AEs, there were more participants in the maraviroc treatment group (59.1%) compared to the efavirenz treatment group (41.1%), who achieved VL suppression < 50 copies/mL at least at two consecutive visits prior to study drug discontinuation due to AEs. Among the discontinuations, the overall duration of treatment was longer in the maraviroc group (range: 4-628 days, median: 173 days, mean: 208.4 days) compared to the efavirenz group (range: 2-480 days, median: 50 days, mean: 119.7 days).

The earlier time to discontinuation in this group compared with the maraviroc group, led to a shorter time period in which to potentially observe true virological failure and the possible selection of non-nucleoside reverse transcriptase inhibitor (NNRTI) and NRTI resistant variants (hypothesis following post hoc analysis).

In the efavirenz treatment group, 8 participants who were discontinued due to AEs developed NNRTI mutations conferring resistance to efavirenz following study drug

discontinuation. Four of these did not suppress to < 50 copies/mL while on study treatment, one of whom developed Y181Y/C mutations while on study drug.

For patients screened as R5, it is likely that any pre-existing D/M/X4 virus has a lower replicative capacity relative to the circulating R5 virus. Maraviroc treatment selectively inhibits the R5-using virus, and (in the absence of other active antiretrovirals) the D/M/X4 virus becomes relatively more fit. When maraviroc selective pressure is removed the circulating R5 virus regains fitness and outgrows the D/M/X4 variants. The time scale for this reversion appears to be within approximately 1 to 3 months of stopping maraviroc treatment.

This reversible and transient selection of pre-existing CXCR4-using virus is very different to the slow emergence of predominantly CXCR4-using virus during the natural history of HIV infection. It is likely that in later stages of HIV infection, CXCR4-using virus emerges as a result of progressive immune dysregulation rather than being a cause of it.

A European regulatory Follow-up Measure requested follow up of viral tropism on all patients failing and remaining in study, with the reversibility of X4-virus (from baseline R-5) to be specifically addressed. An analysis of tropism following failure of maraviroc therapy with CXCR4-using virus in patients with CCR5 virus at baseline, demonstrated that the virus population reverted back to CCR5 tropism in 33 of 36 patients with more than 35 days of follow up.

Evaluator's comment

These points are accepted.

Tropism testing

Enhanced sensitivity Trofile assay

Sponsor's response

The ESTA has not been formally evaluated in large prospective clinical studies. Neither the OTA nor ESTA are FDA-approved assays. The ESTA is only performed by one laboratory in San Francisco with associated inherent time delays. Like OTA, the ESTA requires stringent sample collection, storage and transport requirements as outlined by the vendor (Monogram Biosciences). A minimum volume of 3 mL of plasma is recommended. The assay is validated to a minimum VL requirement of 1000 HIV RNA copies/mL plasma. This poses a challenge for tropism testing in a proportion of patients, such as those with early virological failure (that is, plasma VL < 1,000 copies/mL) or those with undetectable VL who may be seeking to switch treatment for tolerability reasons. In addition, the high cost and relatively long assay turnaround time (approximately two weeks from the time of sample receipt at the Monogram laboratory facility) have also shown to be obstacles in the US to routine tropism evaluation for management of patient treatment options that could include maraviroc, but may be less of a problem in Australia in future. The Australian Government's Medical Services Advisory Committee (MSAC)[13] is assessing the cost effectiveness of funding tropism testing.[14] In the interim, ViiV Healthcare has been funding tests performed prior to commencement of treatment with maraviroc.

[13] An independent expert committee appointed by the Minister for Health and Ageing to strengthen the role of evidence in health financing decisions in Australia.
[14] Consultation Decision Analytic Protocol (DAP) to guide the assessment of a pathology test to determine if a patient has been infected with CCR5 tropic HIV-1 for access to maraviroc. Available at: <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/2C3D39E5008C558ECA2578E100179BCF/$File/Consultation%20DAP%201174.pdf>

Population genotypic tropism testing and clinical outcome

Sponsor's response

For this testing, a population-based consensus sequence is generated. A bioinformatics algorithm is used to interpret the sequence and infer drug susceptibility (Sensitive or Resistant) or tropism (R5 or non-R5). The algorithm(s) used to infer co-receptor tropism are more complex than those for drug resistance, mainly driven by the sequence diversity within the V3 loop, the lack of a signature sequence for co-receptor usage (versus M184V, associated with resistance to lamivudine), and the lack of a gold-standard biological sample that accurately reflects HIV envelope variation within/between a patient(s). Recent advances in both laboratory methodologies to generate high quality V3 loop sequence data and bioinformatics algorithms has greatly advanced the clinical utility of genotypic tropism methods. It should also be noted that, although tropism determinants outside the V3 loop have been described their inclusion in algorithms for tropism determination has not improved prediction of clinical outcome.

Antiviral activity of maraviroc in treatment naïve patients was evaluated in Study A44001026. The clinical response was comparable with maraviroc versus efavirenz in patients classified as R5 by genotype; whereas, the response in patients classified as non-R5 was sub-optimal. Similar findings were obtained when patients were characterised by their ability to achieve HIV RNA < 50 copies/mL plasma.

An analysis of the samples by concordance/discordance was assessed. The concordant R5 group (R5 by both assays) had a good virologic response rate whereas the concordant non-R5 group had a poor virologic outcome. The discordant groups had response rates similar to each other and comparable to that of the R5 concordant group. This observation is taken to suggest that neither ESTA nor population genotype provides a clinically accurate assessment of tropism in every instance; there is no gold standard assay.

Evaluator's comment

According to ViiV Healthcare, genotypic V3 loop testing has superseded ESTA as the routine test available for tropism determination ... (and they state) *The utility of genotypic testing in terms of predicting virological outcomes with maraviroc treatment has been investigated and has been shown to be comparable with ESTA*.

It would have been helpful if the results of Study A4001026 had been analysed in the terms of non-inferiority. If population genotype testing is less sensitive than ESTA then the possibility exists that maraviroc would not prove to be non-inferior in terms of HIV RNA < 50 copies/mL as was the case with the OTA. According to McGovern *et al*., 2010,[15] in the abstract supplied with the applicant's response, approximately 8% of patients in Study A4001026 who screened as R5 by the OTA were classed as X4 by V3-loop sequencing using population based sequencing, compared to the 13.3%-16.1% reclassified using ESTA. The table from the McGovern *et al*., 2010 abstract is reproduced as Table 9, below. However, it is unknown how closely the test used by McGovern *et al.* coincides with commercially available V3 loop tests.

[15] McGovern RA, et al. Population-based Sequencing of the V3-loop Is Comparable to the Enhanced Sensitivity Trofile Assay in Predicting Virologic Response to Maraviroc of Treatment-naive Patients in the MERIT Trial. *17th Conference on Retroviruses and Opportunistic Infections 2010 ;Paper #92British Columbia Center of Excellence, Harrigan Laboratory, Vancouver BC*

Table 9 Maraviroc response by Trofile and V2-loop screening (McGovern *et al.*, 2010)

		Original Trofile		V3 Genotype		ESTA	
		R5	Non-R5	R5	X4	R5	Non-R5
Week 8 Change in plasma VL (log HIV RNA copies/mL)	EFV	-2.8 (353)	n/a	-2.8 (324)	-2.7 (29)	-2.9 (296)	-3.0 (57)
	MVC	-2.7 (352)	n/a	-2.7 (323)	-2.3 (29)	-2.7 (303)	-2.3 (49)
Week 48 <50 copies/mL	EFV	246/353 (70%)	n/a	223/324 (69%)	23/29 (79%)	203/296 (69%)	43/57 (75%)
	MVC	226/352 (64%)	n/a	213/323 (66%)	13/29 (45%)	205/303 (68%)	21/49 (43%)

McGowan and Shah, 2010[16] suggest that genotype based testing has the advantages of lower cost than ESTA, is less technically difficult and has more rapid turnaround time but has lower sensitivity and may miss X4-using strains, may incorrectly identify highly divergent R5 as X4 and miss minority species and lacks clinical trial data.

Geretti and Mackie, 2009[17] state that prospective outcome data for the use of proviral DNA are currently limited, and details of the recommendations about methodology and interpretation are likely to continue to evolve over time. However, one potential advantage of genotypic tropism testing is the ability to circumvent the high plasma VL requirement of phenotypic assays, and evaluate tropism in virologically suppressed patients using proviral DNA. The authors state that there is limited evidence to indicate that genotypic testing of proviral DNA may actually provide better concordance with phenotypic tropism prediction than genotypic analysis of plasma.

Early tropism switch

Sponsor's response

The factors that drive the change in HIV tropism are not clearly understood. Viral evolution and overall change in host immune function and drug pressure (in the context of maraviroc-containing HAART) are potential factors involved.

In Study A4001026 phylogenetic analyses demonstrated that non-R5 variants were a pre-existing viral population as opposed to a recent evolutionary event. Spontaneous tropism changes (from R5 to non-R5 or vice-versa) were observed in approximately l0% of patients between screening and study baseline in the maraviroc clinical trials using the OTA. Where apparent phenotypic tropism changes from R5 to non-R5 occurred, non-R5 virus was generally detectable at the screening time point by more sensitive methods such as 454 "deep sequencing" (Roche 454 GS-FLX) or possibly ESTA.[18]

[16] McGowan JP, Shah S. Understanding HIV Tropism. Published online at Physicians' Research Network www.prn.org: The PRN Notebook Volume 15, January 2010 <http://www.prn.org/index.php/management/article/hiv_infection_in_children>

[17] Geretti AM, Mackie N. Determining HIV-1 tropism in routine clinical practice. 2009. From the British HIV Association Guidelines on HIV-1 tropism Testing, available at <www.bhiva.org/documents/Guidelines/Tropism/HIV-1Tropism.doc>

[18] Brumme CJ, Dong W, Chan D, et al. Short-term variation of HIV tropism readouts in the absence of CCR5-antagonists. Plenary and Oral Posters session presented to the Tenth International Congress on Drug Therapy in HIV Infection November 8, 2010. Available at <http://www.hiv11.com/hiv10/webcast/content/hybrid/O123/download/O123.pdf>

Safety

Sponsor's response

With respect to the clinical significance of change of tropism, there was no evidence in Study A4001026 of detrimental outcomes in patients whose tropism changed and, as there are currently no other antiretroviral agents in this class, there is no concern about cross resistance. There was no evidence of an increase in Category C events or AIDS defining conditions and no increased risk of development of malignancy in the patients who took maraviroc in Study A4001026; and no new or unexpected safety signal were reported from this study.

Although nonclinical data indicate potential for maraviroc to prolong QTc interval at high concentrations a thorough Phase I QT study (A4001016) did not show evidence of clinically significant QT prolongation at doses of 100 mg, 300 mg and 900 mg. Pooled data from Phase I and IIa studies support this finding. Furthermore, clinical data from Phase IIb studies, the pivotal Phase III studies, the expanded access Study A4001050, and post marketing experience to date do not highlight that maraviroc is associated with a clinically significant effect on QTc interval.

In summary, there is currently no evidence that maraviroc has an adverse effect on QT interval or risk of Torsade de Pointes at therapeutic doses. The range of *in vitro*, animal and clinical data has served to characterise the action of maraviroc on cardiac repolarisation and to provide reassurance that maraviroc does not increase the arrhythmogenic risk for humans, even when taking concomitant medication that would increase exposure.

Evaluator's comment

While there is no evidence of increase in Category C events, it is possible that Category C events or deaths occurring during maraviroc treatment are more likely to occur in the presence of X4-using virus, that is, it is possible that the mechanism of development of such events may differ for patients treated with maraviroc versus efavirenz.

Tropism and resistance – Treatment experienced – Week 48

Sponsor's response

A systematic assessment of changes in tropism and impact on virologic, immunologic and clinical outcome is being conducted in the ongoing studies A4001027 and A4001028 in treatment experienced patients. The current report is based on an assessment of these data at Week 48. For those patients with a CCR5 tropism result at baseline, approximately twice as many patients who received maraviroc and failed therapy had a D/M or CXCR4 tropism result at failure compared to a R5-tropism result.

Assessment of $CD4^+$ count at time of failure demonstrated that there was a greater mean increase in $CD4^+$ cell count for patients who failed therapy with maraviroc, even for those patients who failed with CXCR4-using virus, compared to placebo, indicating no adverse effect on $CD4^+$ cell response.

The majority of maraviroc treated patients who had available in-study off-drug (ISOD) follow-up data had reverted back to a CCR5 tropism result at/before their last follow-up visit. This indicates that the virus population in patients failing maraviroc with CXCR4-using virus reverted back to CCR5 tropism after an appropriate time of follow up.

Evaluator's comment

With respect to the statement: *'Assessment of $CD4^+$ count at time of failure demonstrated that there was a greater mean increase in $CD4^+$ cell count for patients who failed therapy with maraviroc, even for those patients who failed with CXCR4-using virus, compared to*

placebo, indicating no adverse effect on CD4+ cell response'. This is considered a generalisation that needs substantiation. It could not be determined from the submitted data, whether the patients who failed maraviroc treatment with CXCR4-using virus had lower CD4+ cell counts at failure than those treated with maraviroc who failed with R5-using virus.

With respect to the ISOD follow-up, it is likely that once a patient has X4-using virus it persists despite inability to detect it.

Change from baseline in VL

Sponsor's response

Of the patients enrolled into Studies A4001027 and A4001028 with an R5 tropism result at screening and who had a tropism result at baseline, 79 (7.6%) had a different tropism result at baseline; all of these were assigned as D/M. The number of patients with a D/M or CXCR4 tropism result at baseline was similar across the three treatment groups (7.7%, 7.5% and 8.3% in the maraviroc QD, maraviroc BID and placebo treatment groups, respectively).

Patients who had a change in tropism assessment from R5 to D/M between screening and baseline had lower median screening CD4+ counts and higher mean screening HIV-1 RNA compared to those whose tropism assessment remained R5. There was no apparent association for screening OSS and duration from diagnosis.

The mean change in HIV-1 RNA for patients who were CCR5 at baseline was -
-2.2 $\log_{10}$ copies/mL in the maraviroc BID group versus –1.04 $\log_{10}$ copies/mL in the placebo group. In patients with D/M tropic HIV-1 at baseline, the mean change in HIV-1 RNA from baseline to Week 48 for maraviroc versus placebo was -1.04 $\log_{10}$ copies/mL versus -1.44 $\log_{10}$ copies/mL.

Evaluator's comment:

Maraviroc treatment of patients with D/M tropism at baseline is, at best, similar to treatment with placebo and possibly worse. It is noted that there is discrepancy between mean and median values, suggesting skewed data, most likely to the left. Numbers with D/M tropism at baseline were small.

Sponsor's response continued

For those patients receiving maraviroc, and who had D/M virus at baseline, the proportion achieving < 400 and < 50 HIV-1 RNA copies/mL is lower compared to those with R5 virus at baseline, in accordance with the findings in study A4001029 in non-CCR5 tropic patients. The proportion achieving HIV RNA < 400 copies/mL by baseline tropism status was, for maraviroc BID versus placebo, CCR5 63% versus 26.2%; and D/M 27.3% versus 29.4%.

The proportion achieving HIV RNA < 50 copies/mL by baseline tropism status was for maraviroc BID versus placebo, CCR5 49.6% versus 19.8%; and D/M 27.3% versus 17.7%.

Evaluator's comment

It is considered unusual that the proportion of the maraviroc BID treated group with D/M tropism at baseline achieving HIV RNA < 400 copies/mL is identical to that achieving < 50 copies/mL.

Changes in tropism result at treatment failure

Sponsor's response

Of the 252 patients with a CCR5 tropism result at baseline and who experienced treatment failure, 82 (32.5%) had a change in tropism result to CXCR4 or D/M at the time of treatment failure. All but 6 of these patients were in the maraviroc (QD and BID) treatment arms.

Evaluator's comment

This is in keeping with selective pressure of treatment with a CCR5 receptor antagonist.

Change in $CD4^+$ count at failure by tropism at failure

Sponsor's comment

There was a greater increase in $CD4^+$ cell count from baseline to Week 48 for both maraviroc treatment groups compared with placebo (116.0, 124.1 and 60.9 cells/μL for maraviroc QD, maraviroc BID and placebo, respectively).

For those patients with a CCR5 tropism result at baseline, more patients who received maraviroc and failed therapy had a D/M or CXCR4 tropism result at failure (n = 76) compared to a CCR5 tropism result (n = 57). The mean increase in $CD4^+$ cell count from baseline in patients who failed with a change in tropism to D/M tropic or CXCR4, in both the maraviroc QD (47 cells/μL) and BID (57 cells/μL) groups was greater than that seen in the total placebo group who failed (25 cells/μL). Increases of mean changes in $CD4^+$ cell counts for the maraviroc treatment groups were also seen for 37 patients with a non-CCR5 tropism result at baseline (D/M, CXCR4 or non-phenotypable), and for 18 patients with a CCR5 tropism result at baseline but who had no tropism assignment at failure.

Patients failing with CXCR4-using virus fail approximately 50 days earlier than those failing with CCR5 tropic virus. Patients in the maraviroc BID group who failed with R5 had mean $CD4^+$ cell count 133.1 cells/μL compared to those who failed with D/M tropism (57.2 cells/μL). The sponsor considers that, taken together, the results do not indicate an adverse effect on $CD4^+$ cell count in patients failing a maraviroc containing regimen compared to those failing on placebo plus OBT, even in the context of failure with a CXCR4-using virus.

Evaluator's comment

The difference between means and medians and the large standard deviations and wide CIs suggest skewed and widely spread data and reflect small sample sizes. However, it appears likely that failure with X4-using virus is associated with a reduction in $CD4^+$ cell count. As results are based on LOCF, it is also possible that the $CD4^+$ cell count at failure is underestimated. Furthermore it would be important to know what happens to the $CD4^+$ cell count of the two tropism populations beyond the time of failure; that is, whether the lower $CD4^+$ cell count represents a marker of possible reduced response to further therapy.

In-study off-drug follow up

Sponsor's response

An analysis of tropism assessment over time (following discontinuation of study drug) was performed for all patients with CCR5 tropic virus at baseline who failed with CXCR4-using virus and remained in study off drug (ISOD), in order to evaluate rates of reversion to baseline tropism. At Week 48, tropism reverted back to CCR5 in all but 3 of 36 maraviroc treated patients with tropism follow-up of more than 35 days duration.

Between the Week 48 and Week 96 assessments, 8 patients (who had CCR5 tropic virus at baseline) discontinued due to loss of efficacy with CXCR4-using virus. For the one patient with tropism follow-up data of more than one month, the virus reverted to CCR5 tropism during follow up.

These data are taken to indicate that in patients with CCR5 tropic virus at baseline who failed in Studies A4001027 and A4001028 with CXCR4 or D/M tropic virus, the virus population reverted back to CCR5 tropism after an appropriate time of follow up. These data are considered consistent with the selective and reversible suppression of CCR5 tropic viruses during maraviroc therapy.

Evaluator's comment

The submitted data support the conclusions that, of those patients with available tropism results, most patients whose virus changed tropism to include X4-using virus under the selective pressure of maraviroc treatment reverted to R5 when the pressure was removed. However, not all patients were demonstrated to revert to R5 and the conclusion appears to be based on incomplete data. As tropism has previously been demonstrated to be labile within the short interval between screening and baseline, and as X4-using virus is not considered a mutation but rather a pre-existing strain, it seems likely that X4-using virus persists and the time of sampling may influence the result of tropism testing.

Category C infections

Sponsor's response

In general, very few Category C events occurred in these studies and there is no evidence of an excess of Category C malignancies or infections in patients receiving maraviroc compared to placebo. For the Week 48 data cut-off: 7 patients with CCR5 tropic virus at baseline and who experienced a category C event had emergence of CXCR4-using virus at the time of the event (4 on maraviroc QD, 2 on maraviroc BID and 1 on placebo). Five of these events were infections (3 patients with candidiasis, 1 with pneumonia and 1 with herpes proctitis), all occurring in patients receiving maraviroc. The other maraviroc treated patient was diagnosed with AIDS encephalopathy and the placebo patient developed Kaposi's sarcoma. Six of the 7 patients had a baseline CD4+ count of < 20 cells/μL and were therefore at high risk of developing a Category C event. The seventh patient (with herpes proctitis) had a baseline CD4+ count of 186 cells/μL. This analysis supports the conclusions from the Week 24 data that there is no indication of a correlation between emergence of CXCR4-using virus and development of Category C events.

Evaluator's comment

Not all patients had a tropism result available for the time of diagnosis of the Category C event. Of those with available data:

- 10 of 30 (33%) in the maraviroc QD group had non-R5 at the time of diagnosis of the event, 6 of whom had non-R5 at baseline.
- 7 of 22 (32%) patients in the maraviroc BID group had non-R5 at the time of diagnosis of the event; 4 had non-R5 at baseline.
- 17 of 52 (33%) overall treated with maraviroc had non-R5 at the time of diagnosis; 7 of the 52 (13%) had R5 at baseline and changed tropism.
- 4 of 18 (22%) in the placebo group had non-R5 at the time of diagnosis of the event; 3 had non-R5 at baseline and 1 of the 18 (6%) transitioned from R5 to non-R5.

Analysis of the data is post hoc and based on relatively small numbers and can potentially be used to support differing hypotheses. It could be argued that the proportions with

non-R5 tropism at the time of Category C event appears disproportionately high considering the overall numbers at baseline and the numbers transitioning from R5 overall.

Treatment failure with CCR5 tropic virus

Sponsor's response

A preliminary investigational study of *in vivo* maraviroc resistance (conducted during the blinded phase of the Phase III clinical program) identified plateaus in dose response curves as a phenotypic marker of resistance for 4 patients who received maraviroc as part of an optimised background regimen and who failed blinded therapy with a CCR5 tropic virus. A more complete analysis has now been conducted on all 59 patients who failed maraviroc therapy with a CCR5 tropic virus by Week 48.

The findings of these studies are:

- Maraviroc resistance, defined as dose response curves with plateaus in MPI < 95% in the phenotypic assay, was identified for 22/59 patients at failure.
- Shifts in the concentration at which *in vitro* viral replication was inhibited by 50% (IC_{50}), in the absence of any plateau in dose response, did not appear to be a reliable phenotypic marker of resistance.
- Clonal gp160 sequencing for 16 patients identified amino acid substitutions/mutations in the V3 loop of the maraviroc resistant viruses.
- No signature mutations of maraviroc resistance were identified, implying multiple genetic pathways to resistance may exist and the mutations may be virus-specific.
- Maraviroc resistance was primarily observed in patients who had no fully active drugs present in their OBT at baseline.

Incomplete adherence to their drug regimen, as evidenced by inspection of the maraviroc plasma concentrations (obtained during periodic PK sampling) or by documented treatment interruption, accounted for virological failure in the majority of patients who failed treatment with a CCR5 tropic virus that did not appear to be maraviroc-resistant.

Evaluator's comment

These points are accepted.

Second round benefit risk assessment

Benefits

- Maraviroc 300 mg BID demonstrated a better safety profile than efavirenz with respect to discontinuations due to AEs and with respect to lipid profile (cholesterol, LDL and triglycerides).
- Depending on the criteria for identification of non-C5 tropic virus, and in combination with zidovudine/lamivudine, maraviroc efficacy in terms of VL < 50 copies/mL was either statistically non-inferior to efavirenz, or nearly so.[19]

Risks

- In patients with viral failure there appeared to be an increased risk of development of resistance to the two agents used in the OBT, in particular to lamivudine and in

[19] As recommended by the *Guideline on the Clinical Development of Medicinal Products for the Treatment Of HIV Infection*. Reference EMEA/CPMP/EWP/633/02, which has been adopted in Australia

particular in the presence of CXCR5-using virus. However this is an observational finding and it is also accepted that the M184V mutation may not necessarily preclude useful, continuing treatment with lamivudine.

- The commercially available ESTA requires a VL of at least 1,000 copies/mL, which may limit the early detection of X4-using virus. The length of time required for the assay turnaround is a practical consideration, as is the cost of the assay. Use of the ESTA is specified in both the US and the Canadian *Indications* for maraviroc.
- The alternative genotype based tropism test method appears to have lower sensitivity than the ESTA and lacks the supporting clinical trial data.
- $CD4^+$ cell counts for maraviroc treated patients who failed treatment and demonstrated transition from R5- to X4-using virus were noted to have lower $CD4^+$ cell counts than those who failed maraviroc treatment with R5-using virus.
- Not all non R5-using viruses were demonstrated to revert to R5 when maraviroc treatment was stopped.
- No increased risk of progression to AIDS or increased resistance to HIV treatment has been numerically demonstrated. However, the studies were not specifically designed to demonstrate individual response to change of viral tropism. The possibility that Category C AIDS events in maraviroc treated patients are more likely to occur in the presence of non-R5-using virus cannot be excluded. Viral tropism data for those patients who died could not be located in the submission.

Benefit-risk balance

The balance is considered to lie on the side of benefit.

Second round recommendation regarding authorisation

It is recommended that maraviroc is registered for use in treatment naïve patients. It is recommended that the Delegate considers the requirement to include the conditions specified in the US and Canadian product information for maraviroc, including the requirement for diagnosis of R5-using viral infection by means of the ESTA.

The clinical evaluator's recommended revisions to the PI are beyond the scope of this AusPAR.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP; version 1.6, dated 30 September 2010) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

Subject to the evaluation of the nonclinical aspects of the Safety Specification (SS) by the Toxicology area of the TGA Office of Scientific Evaluation (OSE) and the clinical aspects of the SS by the Office of Medicines Authorisation (OMA), the summary of the ongoing safety concerns as specified by the sponsor is as shown in Table 10:

Table 10. Ongoing safety concerns

Important identified risks	None
Important potential risks	Potential to alter immune function: Infections: including common viral and bacterial infection, viral encephalitides, TB reactivation, chronic hepatitis B/C, Category C infections Malignancies Autoimmune diseases Potential for hepatic toxicity Change in HIV tropism assessment Ischaemic cardiac disorders Off-label use in children and adolescents and pregnant women Muscle disorders such as rhabdomyolysis and myositis
Important missing information	Pregnant women Paediatric and adolescent population

Other Risks

Other identified Risks	Pregnant women Paediatric and adolescent population

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities, consistent with the activities outlined in *3.1.2 Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03),* to monitor all the specified ongoing safety concerns. In addition the sponsor proposes to further monitor the following specified ongoing safety concerns (except pregnant women and off-label use) by analysing data from on-going studies:

- Hepatic safety
- Potential to alter immune function: Infection (including Category C events, HCV co-infection, encephalitides)
- Potential to alter immune function: malignancies
- Potential to alter immune function: autoimmune diseases
- Change in tropism result from CCR5 to CXCR4 tropic with associated adverse clinical outcome
- Potential imbalance in ischaemic cardiac events
- Potential for rhabdomyolysis and myositis
- Off label use in paediatrics and adolescents

- Pregnant women

The sponsor provided a list of outstanding studies within the Pharmacovigilance Plan, including milestones.

The sponsor states that the Targeted Follow-Up Questionnaires (TFupQ) are routinely used to gather specific information on serious AEs reported spontaneously for maraviroc. The events were selected based on the potential risks identified in the RMP and, for maraviroc, comprise:

- Infections (that is, Category C infections and encephalitis)
- Malignancies (AIDS and non-AIDS related)
- Life threatening liver related events, ischaemic cerebrovascular and cardiovascular events
- Rhabdomyolysis and myositis.

The sponsor also reports that hepatic data will be reviewed by the Hepatic Expert Panel or its members on request by the sponsor or the Data Safety Monitoring Board (DSMB); and an Immune Expert Panel (one for infections and one for malignancy) will be convened if there is any evidence that malignancy rates or rates of Category C infections exceed those expected.

Risk minimisation activities

Routine risk minimisation activities will include contraindications, special warning and precaution statements, instructions for use, overdosage statements and/or notification of undesirable effects in the Australian PI for all the specified ongoing safety concerns. In relation to the important potential risk: *'Change in tropism result from CCR5 to CXCR4 tropic with associated adverse clinical outcome'* the sponsor has developed educational material for prescribers on the understanding of genotypic tropism testing.

Summary of initial recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted RMP is applicable without modification in Australia unless so qualified:

- The non-clinical and clinical aspects of the SS remain subject to the evaluation by the Toxicology area of the OSE and by the OMA respectively.
- Based on the results of Study A4001026, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) was concerned by the high risk for virological failure and resistance development in the treatment of CCR5 tropic HIV-1 infected adult antiretroviral-naïve patients with maraviroc. Furthermore the important potential risk: *'Development of drug resistance'* is common for other antiretroviral medicinal products. Consequently the sponsor should amend the relevant sections of the RMP to include the important potential risk: *'Development of drug resistance'* as an ongoing safety concern or provide compelling justification for not doing so.
- The sponsor should consider amending the important missing information: *'Pregnant women'* to *'Pregnant or lactating women'*, as use during lactation already appears to be encompassed under this heading. The relevant sections of the RMP should be amended accordingly.

- In principle there is no objection to the sponsor implementing additional pharmacovigilance activities to further monitor the specified ongoing safety concerns. However, the ongoing studies are not considered to be part of the planned clinical studies in the pharmacovigilance plan. Therefore the related study protocols have not been reviewed. The sponsor has recently provided the final protocol of the planned study in patients co-infected with HCV (A4001098) and advised that this study was initiated on 18 May 2011. Consequently it is also not considered to be part of the planned clinical studies in the pharmacovigilance plan and the related study protocol has not been reviewed. Nevertheless an update on the progress/results/analysis of these studies, as outlined in the RMP, will be expected in future Periodic Safety Update Reports (PSURs).
- The final protocol for Study A4001098 should be included in Annex 5 of the RMP.
- The sponsor should provide copies of the specified Targeted Follow-Up Questionnaires, and include these in Annex 7 of the RMP.
- If the important potential risk: *'Development of drug resistance'* is included as an ongoing safety concern, monitoring by routine pharmacovigilance is acceptable.
- The educational plan for prescribers on the understanding of genotypic tropism testing is considered to be an additional risk minimisation activity. Consequently the sponsor should amend the table *'A Summary Table of Planned Actions'* to indicate that routine risk minimisation activities alone are insufficient to appropriately mitigate the specified ongoing safety concern and to reflect the proposed use of additional risk minimisation activities for such purpose.
- Given the Australian and international post marketing exposure of maraviroc, the sponsor should provide information on the occurrence and frequency of medication errors from related PSURs. Consequently, the section on *'Potential for Medication Errors'* of the RMP should be amended accordingly.
- The sponsor has recently advised that educational materials on the understanding of genotypic tropism testing are provided to prescribers in Australia. Consequently the sponsor should provide details of this educational plan and include them in Annex 8 of the RMP.
- The sponsor must also plan appropriate methods to assess the effectiveness of this additional risk minimisation activity as a measure to reduce the important potential risk: *'Change in tropism result from CCR5 to CXCR4 tropic with associated adverse clinical outcome'* in the post market environment and provide details of these methods to the TGA for review.
- In regard to the proposed routine risk minimisation activities, if the important potential risk: *'Development of drug resistance'* is included as an ongoing safety concern it is recommended to the Delegate that the draft PI document be revised to include a similar statement to that found in the currently approved Summary of Product Characteristics (SmPC): *"Background resistance to other classes of antiretrovirals have been shown to be similar in previously undetected CXCR4 tropic virus of the minor viral population, as that found in CCR5 tropic virus."*
- The nonclinical and clinical aspects of the PI remain subject to the evaluation by the Toxicology area of the OSE and by the OMA respectively.
- In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft CMI document be revised to include a warning that the product is not to be used in children to adequately reflect the currently approved Australian PI.

The sponsor subsequently provided information and documents that addressed all the above matters to the satisfaction of the TGA.

Final recommendation

If this application is approved the following specific condition of registration should be applied: The RMP version: 1.6, dated 30 September 2010, to be revised as specified in the sponsor's correspondence to TGA dated 21 July, 12 and 18 August 2011, must be implemented.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Delegate considerations

Supporting data

Clinical data only are submitted. The submitted data include:

- 48 Week and 96 Week results of Study A4001026 for treatment naïve patients
- 48 Week results of two pivotal studies (A4001027 and A4001028) in treatment experience patients
- 48 Week results for supportive Study (A4001029) assessing the safety of maraviroc in treatment experienced patients infected with non-CCR5 tropic or non-phenotypable HIV-1.

The Week 48 efficacy analysis in treatment experienced patients from Studies A4001027 and A4001028 confirmed the superior efficacy of maraviroc 300 mg QD and BID compared to placebo, and the safety analysis revealed no new or unexpected safety signals. The safety follow-up of 48 Weeks is considered relatively short, and rare AEs may remain to be identified. The clinical evaluator agrees that the risk benefit profile remains positive in these treatment experienced patients. The PI amendments recommended by clinical evaluator in relation to treatment experienced patients have been largely accepted by the sponsor. The 48 Week results of supportive Study A4001029 were also included in the PI, but the use of maraviroc for the treatment of patients infected with non-CCR5 tropic virus is not proposed.

This application concerns an extension of indication to treatment naïve patients infected with CCR5 tropic HIV-1; therefore only Study A4001026 is discussed in this overview.

Study A4001026 (MERIT Study)

Study A4001026 was a Phase IIb/III multicentre, randomised (1:1:1), double-blind study comparing maraviroc 300 mg either QD or BID versus efavirenz 600 mg QD, each in combination with lamivudine 150 mg/zidovudine 300 mg (Combivir) BID, in treatment naïve, CCR5 tropic, HIV-1 infected patients. Results to Week 96 were initially provided. There was an interim analysis at Week 16, a primary efficacy analysis at Week 48, and an analysis at Week 96. The analysis at Week 240 was later submitted as supplementary data.

Eligible patients were HIV-infected subjects who were ≥ 16 years old and who had > 2000 copies of HIV-1 RNA/mL. Infection with CXCR4 (X4) or D/M tropic virus and resistance to efavirenz, zidovudine or lamivudine were exclusion criteria. The OTA was used to detect the presence of CXCR4- tropic virus. Detailed criteria for subject's selection were included. All subjects had genotypic and/or phenotypic testing for the presence of CCR5 tropic HIV-1 prior to receiving study treatments.

A total of 695 patients were treated: 174 in the maraviroc QD group, 360 in the maraviroc BID group, and 361 in the efavirenz group. Following the interim analysis at Week 16, the maraviroc QD group was discontinued due to failure to meet non-inferiority criteria. Subjects in the maraviroc QD arm were eligible to receive OL maraviroc 300 mg BID, based on safety criteria and virological response. The efficacy analysis discussed in this overview is focused on the comparison between subjects treated with maraviroc 300 mg BID (referred to here as the maraviroc BID group) and subjects treated with efavirenz 600 mg QD (the efavirenz QD group).

The co-primary efficacy endpoints are proportion of subjects achieving HIV RNA VL < 400 and < 50 copies/mL at Week 48. The primary objective was to assess non-inferiority of maraviroc BID compared to efavirenz QD in terms of the proportion of subjects achieving VL < 400 and < 50 copies/mL at Week 48. Similar assessments were conducted at Weeks 24 and 96 as secondary objectives. Other secondary objectives included: comparison of treatment effects on TLOVR, reduction of plasma $\log_{10}$ VL from baseline, changes in $CD4^+$ and $CD8^+$ cell counts from baseline, Time-Averaged Difference (TAD) in $\log_{10}$ VL, HIV-1 genotype and phenotype at the time of failure, HIV-1 tropism at baseline and at the time of failure, safety, and tolerability.

The primary analysis was based on 1-sided, 97.5% CI with adjustment for randomisation strata. Non-inferiority was concluded if the LB of 97.5% CI was above -10%. For the primary analysis, subjects were stratified by geographic location (Northern or Southern Hemisphere) and screening VL (< 100,000 or ≥ 100,000 copies/mL). Efficacy analyses were conducted in the FAS and the PP set. Sensitivity analysis was performed using the TLOVR algorithm. The initially planned 1-sided significance level of 0.0125 (Bonferroni adjustment for multiple comparisons) was changed to the 1-sided 97.5% CI when the maraviroc QD group was discontinued.

Results

A relatively high proportion of females (29% of the maraviroc group, 28% of the efavirenz group) and Black patients (34.2% of the maraviroc group and 36.8 % of the efavirenz group) were included in the study. No significant differences in demographic characteristics were noted between the two arms. The overall rates of study discontinuation were similar in the two arms. However, the efavirenz group had higher rates of discontinuation due to AEs (13.6%) compared with the maraviroc arm (4.2%), whereas the maraviroc group experienced higher rates of virologic failure (11.9%) compared to the efavirenz group (4.2%).

Efficacy analyses based on the original Trofile assay

Proportion of subjects achieving VL < 400 and < 50 copies/mL

Week 48 analyses in FAS: Based on achieving VL < 400 copies/mL, the percentage of subjects was 70.6% for the maraviroc group and 73.1% for the efavirenz group. The LB of 1-sided 97.5% CI for the difference was -9.5%, which fulfilled the non-inferiority criteria. Non-inferiority is also supported by the TLOVR sensitivity analysis.

Based on achieving VL < 50 copies/mL, the percentage of subjects was 65.3% in the maraviroc group and 69.3% in the efavirenz group. The LB of the 1-sided 97.5% CI for the difference was -10.9%, which failed to meet the non-inferiority criteria. The TLOVR sensitivity analysis was consistent with this finding. The results are summarised in Tables 11 and 12, below.

Table 11. Percentage of subjects with VL< 400 and < 50 copies/mL at Week 48 in the FAS

Parameter	Maraviroc 300 mg BID N=360	Efavirenz 600 mg QD N=361
<400 copies/mL at Week 48	70.6% (n=254)	73.1% (n=264)
<50 copies/mL at Week 48	65.3% (n=235)	69.3% (n=250)

N= number of subjects in the treatment group in the indicated population
n = number of subjects contributing to the calculation of the percentage

Table 12. Differences in percentage of subjects with VL< 400 and < 50 copies/mL at Week 48 in the FAS

Maraviroc 300 mg BID versus efavirenz 600 mg QD	Difference in Percentages[a]	
	Difference in Percentages	Lower Bound of 1-Sided 97.5% CI
Viral Load <400 copies/mL	-3.0	-9.5
Viral Load <50 copies/mL	-4.2	-10.9

a: adjusted for randomisation strata

Week 48 analyses in the PP set: the LB of the 1-sided 97.5% CI for the difference between the two treatment arms was -10.5% and -11.2% based on VL < 400 and <50 copies/mL, respectively. Non-inferiority criteria were not met.

Week 96 analyses in the FAS: based on achieving VL < 400 copies/mL, the percentage of subjects was 61% for the maraviroc group and 65% for the efavirenz group. Based on achieving VL < 50 copies/mL, the percentage of subjects was 57% and 63% for the maraviroc and efavirenz group, respectively. The LB of the 1-sided 97.5% CI for the difference was -10.2 and -12.8 based on VL < 400 and < 50 copies/mL, respectively. The pre-specified non-inferiority criteria were not met.

Mean change from baseline in CD4⁺ cell count

At Week 48: the mean increase from baseline in CD4⁺ cell count was greater in the maraviroc group than in the efavirenz group (170 versus 144 cells/mm^3). The difference was 26.3 cells/µL (95% CI 7.0, 45.6). Results for the PP population supported this finding.

At Week 96: the mean difference in CD4⁺ cell count between the maraviroc and efavirenz groups was 35.44 cells/µL. The 95% CI (13.2, 57.86) excluded zero, indicating a better result for maraviroc BID than for efavirenz QD.

Virologic failure and rebound

Week 48 assessment: based on VL < 400 copies/mL, virologic failure occurred in 27.7% of the non-responders in the maraviroc group, compared to 5.3% of the non-responders in the efavirenz group. Virologic failure based on VL < 50 copies/mL occurred in 32.0% of the non-responders in the maraviroc group, compared to 8.8% in the efavirenz group.

Rebound based on VL < 400 copies/mL was reported for 20.8% of non-responders in the maraviroc group compared to 16.0% in the efavirenz group. Rebound based on VL

< 50 copies/mL occurred in 19.7% of non-responders in the maraviroc group compared to 14.7% in the efavirenz group.

Week 96 assessment: A similar pattern to that in Week 48 was demonstrated for virologic failure and rebound assessed at Week 96.

Overall, the rates of virologic failure and rebound were higher in the maraviroc BID group.

Viral resistance at the time of discontinuation / treatment failure

Week 48 assessment: At the time of discontinuation, 33/97 (34.0%) in the maraviroc group and 3/91(3.3%) in the efavirenz group had resistance to lamivudine. Six of 97 subjects (6.2%) in the maraviroc group had virus with zidovudine resistance, evidenced by the presence of one or more TAMs. For all 6 patients whose virus had TAMs, lamivudine resistance was also present. None of the 91 subjects who failed efavirenz had virus with TAMs. Eight of 91 (8.8%) in the efavirenz group had resistance to efavirenz. No subjects in the maraviroc group had resistance to efavirenz.

At the time of treatment failure, 62.8% (27/43) in the maraviroc group and 20.0% (3/15) in the efavirenz group had resistance to lamivudine. In addition, 14.0% (6/43) in the maraviroc group had zidovudine resistance. For all 6 subjects whose virus had TAMs, lamivudine resistance was also present. None of the 15 subjects who failed efavirenz had virus with TAMs at failure. Seven of 15 subjects (46.7%) in the efavirenz group had resistance to efavirenz at time of failure. No subjects in the maraviroc group had reduced susceptibility to efavirenz.

Week 96 assessment: At the time of discontinuation, 40 (31.0%) in the maraviroc group and 8 (6.5%) in the efavirenz group had resistance to zidovudine/lamivudine. Six (4.7%) subjects in the maraviroc group and 2 (1.6%) in the efavirenz group had virus with one or more TAMs.

At the time of treatment failure, 33 (60.0%) subjects in the maraviroc group and 8 (34.8%) in the efavirenz group had resistance to zidovudine/lamivudine. In addition, 6 (10.9%) in the maraviroc group and 2 (8.7%) in the efavirenz group had virus with one or more TAMs.

Overall, a higher percentage of patients in the maraviroc group developed resistance to backbone antiviral agents.

Viral tropism at the time of discontinuation / treatment failure

Of the 694 evaluable subjects, 13 (3.8%) in the maraviroc group and 11 (3.1%) in the efavirenz group switched from CCR5 tropic at screening to D/M tropic at baseline.

Week 48 assessment: at the time of discontinuation, 75 patients in the maraviroc group and 74 in the efavirenz group had a CCR5 tropism result at baseline and on-treatment. Of these, 12 subjects, all in the maraviroc group, had a change in tropism to CXCR4 or D/M. At the time of treatment failure, 32 subjects in the maraviroc group and 15 in the efavirenz group had a CCR5 tropism result at baseline and on-treatment. Of these, 10 subjects, all in the maraviroc group, had a change in tropism to CXCR4 or D/M.

Week 96 assessment: at the time of discontinuation, 106 subjects in the maraviroc group and 105 in the efavirenz group had a CCR5 tropism result at baseline and on-treatment. Of these, 14 subjects, all in the maraviroc group, had a change in tropism to CXCR4 or D/M.

At the time of treatment failure, 43 subjects in the maraviroc group and 22 in the efavirenz group had a CCR5 tropism result at baseline and on-treatment. Of these, 12 subjects, all in the maraviroc group, had a change in tropism to CXCR4 or D/M.

It appears that maraviroc treatment failure may increase the risk of selection of non-CCR5 tropic virus; however, the majority of the subjects who failed with maraviroc still had CCR5 tropic virus at the time of treatment failure.

Tropism and viral resistance

Week 48 assessment: in the maraviroc group, 7/13 (54%) who failed with CCR5 tropic virus had zidovudine/lamivudine resistance, compared to 16 of 16 (100%) subjects who failed with D/M or CXCR4 tropic virus. All viruses with zidovudine/lamivudine resistance at failure contained the M184V/I mutation with or without additional NRTI resistance mutations.

Week 96 assessment: zidovudine/lamivudine resistance mutations were reported by 10 (18.2%) subjects in the maraviroc group and 5 (21.7%) subjects in the efavirenz group who had CCR5 tropism at the time of failure. Of these, the M184V/I mutation was present in 10 (18.2%) of the maraviroc group and 5 (21.7%) of the efavirenz group. Nine (39.1%) in the efavirenz group developed efavirenz associated mutations. Of those with D/M tropism at the time of treatment failure in the maraviroc group, 14 (25.5%) had zidovudine/lamivudine mutations and 14 (25.5%) had an M184V/I mutation.

Tropism and $CD4^+$ cell count

Week 48 assessments: Change from baseline in $CD4^+$ cell count was higher across all tropism groups for the maraviroc group compared to the efavirenz group for those failing treatment. Mean $CD4^+$ cell count increases from baseline were greater in all maraviroc treatment failures (100.6 cells/μL) compared with all efavirenz treatment failures (44.3 cells/μL). Subjects with D/M tropic or CXCR4 virus at the time of maraviroc treatment failure had mean increases in $CD4^+$ cell count (83.3 cells/μL) that were similar to those who failed maraviroc with CCR5 tropic virus (80.3 cells/μL).

Week 96 assessment: the $CD4^+$ cell count increased from baseline for subjects in the maraviroc group who were either CCR5 tropic or CXCR4 tropic at treatment failure. Mean increases in $CD4^+$ cell count were higher for those who were CCR5 tropic at treatment failure compared with those who were CXCR4 tropic at treatment failure.

Subgroup analysis

In the stratum with VL at screening ≥ 100,000 copies/mL, the proportions of subjects achieving VL < 400 and < 50 copies/mL were lower in the maraviroc group compared to the efavirenz group. Poorer response rates were also observed for the maraviroc group in Black subjects, in Southern hemisphere patients, in patients with subtype C virus and in female subjects.

Re-analysis of efficacy using ESTA

Following the Week 96 database lock, an ESTA became available and the OTA was replaced by ESTA in the market. Data from *in vitro* experiments showed that ESTA has increased sensitivity in detecting CXCR4 tropic virus. A retrospective re-analysis of efficacy was conducted on the subpopulation of subjects who were identified as CCR5 positive based on ESTA. The efficacy endpoint for this analysis was the percentage of subjects with VL < 400 and < 50 copies/mL at Week 96.

Of the 721 subjects in both arms of the study with virus originally classified as CCR5 at the screening, 106 (14.7%) were re-classified as D/M tropic or X4 tropic by ESTA; 48 (13.3%) and 58 (16.1%) in the maraviroc and efavirenz arms, respectively. On re-analysis, discontinuations due to lack of efficacy were 9.3% in the maraviroc group versus 4% in the efavirenz group. However the rate of discontinuation differed depending on the analysis method used. Using the TLOVR algorithm for the FAS, non-responders due to virologic failure were 21.3% in the maraviroc group compared to 4.9% in the efavirenz group. Non-responders due to rebound were 22.5% in the maraviroc group compared to 16.0% in the efavirenz group. Non-responders due to AEs were 15.0% in the maraviroc group versus 53.1% in the efavirenz group. Similar patterns were seen at 96 Weeks.

Week 48 assessment: the re-analysis in FAS showed that 68.5% in the maraviroc arm and 68.3% in the efavirenz arm reached VL < 50 copies/mL, resulting in a difference of -0.2% with a LB of 97.5% CI of -7.4%. The non-inferiority criterion was fulfilled, and this was supported by the PP analysis (LB of CI -9.8%). For VL < 400 copies/mL, the re-analysis in FAS showed a difference of + 0.6, with a LB of 97.5% CI of -6.4%, fulfilling the non-inferiority criteria. This was also supported by PP analysis (LB of CI:-9.5). Results are summarised in Table 13, below.

Table 13. Week 48: Percentage of subjects with VL < 400 and < 50 copies/mL in the FAS

		Maraviroc 300 mg BID % (n/N)	Efavirenz 600 mg QD % (n/N)	Difference in %		
				Difference in Percentages	Lower Bound of 1-Sided 97.5% CI	Lower Bound of 1-Sided 98.75% CI
Week 48						
<400 copies/ml	Trofile	70.6% 254/360)	73.1% (264/361)	-3.0	-9.5	-10.4
	Enhanced Trofile	73.3% (228/311)	72.3% (219/303)	0.6	-6.4	-7.4
<50 copies/ml	Trofile	65.3% (235/360)	69.3% (250/361)	-4.2	-10.9	-11.9
	Enhanced Trofile	68.5% (213/311)	68.3% (207/303)	-0.2	-7.4	-8.4

Week 96 assessment: the percentage of subjects with VL < 400 and < 50 copies/mL at Week 96 in the FAS set is presented in Table 14, below.

Table 14. Week 96: Percentage of subjects with VL < 400 and < 50 copies/mL in the FAS

Parameter	Maraviroc 300 mg BID (N=360)	Efavirenz 600 mg QD (N=361)
<400 copies/mL at Week 96	61.4% (n=221)	64.5% (n=233)
<50 copies/mL at Week 96	56.9% (n=205)	62.6% (n=226)

N = number of subjects in treatment group' n = number of subjects with an observation

The difference between the two arms in the percentage of subjects with VL <400 and < 50 copies/mL was -3.2 and -5.8, respectively. The LB of 97.5% CI for the difference was -10.2 and -12.8, respectively, which failed to meet the non-inferiority criteria.

Various sensitivity analyses for both VL < 400 and < 50 copies/mL at 48 and 96 Weeks failed to support non-inferiority.

Efficacy analyses at Week 240 from Study A4001026

The efficacy analyses at Week 240 were provided in the supplementary data. Based on ESTA analysis and with the VL cut-off of 50 copies/mL, the percentage of subjects was 50.8% (158/311) in the maraviroc group and 45.9% (139/303) in the efavirenz group. Based on the OTA analysis, the percentage of subjects was 48.9% (176/360) in the maraviroc group and 45.1% (165/361) in the efavirenz group.

At Week 240, the mean changes from baseline in $CD4^+$ cell count by visit (LOCF) was 292.9 cells/µL for the maraviroc BID group and 270.6 cells/µL for the efavirenz QD group.

Safety data from Study A4001026 for treatment naïve patients

The safety of maraviroc BID compared to efavirenz QD, each in combination with zidovudine/lamivudine, in treatment naïve patients was assessed to Week 96. The total exposure, in patient-years, was 506 years for maraviroc and 507.9 years for efavirenz. The median duration of exposure was 672 days for maraviroc and 673 days for efavirenz.

All causality AEs were reported by 399 (94.2%) of the maraviroc BID group and 342 (94.7%) of the efavirenz group. Treatment related AEs were reported for 65.8% of the maraviroc group and 79.2% of the efavirenz group. The most frequently reported treatment emergent AEs were nausea (36.1% for maraviroc, 34.6% for efavirenz), headache (25.3% for maraviroc, 25.2% for efavirenz), diarrhoea (8.1% for maraviroc,

12.7% for efavirenz) and fatigue (16.1% for maraviroc and 14.1% for efavirenz). The incidence of Grade 3 treatment emergent AEs was greater in the efavirenz arm. However, the incidence of Grade 4 events was similar for both treatment arms.

A total of 94 subjects permanently discontinued from the study due to treatment emergent AEs; the percentage of patients who discontinued the study due to AEs was lower in the maraviroc group (7.5%) compared to that in the efavirenz group (18.6%). The most common reasons for discontinuation were increased transaminases, nausea and pregnancy in the maraviroc group, and rash, pregnancy, tuberculosis, dizziness and nausea in the efavirenz group.

Twelve subjects died (6 in each treatment group) during the study, up to the Week 96 cut-off. Two deaths were considered to be related to the study drug, both in the maraviroc group: one case of nasopharyngeal cancer reported on Day 502, and one case of diffuse large B-cell lymphoma reported on Day 268.

Forty-eight (13.3%) subjects in the maraviroc group and 55 (15.2%) in the efavirenz group recorded treatment emergent serious AEs during the 96 Week treatment period, or within 7 days of study drug discontinuation. Serious AEs were considered related to the study drug for 10 (2.8%) of the maraviroc group and 15 (4.2%) of the efavirenz group, and no clear pattern of events was discernable.

Adverse events of interest include infections, AIDS related events and malignancies. A similar percentage of participants reported treatment related AEs relating to infections and infestations.

Treatment emergent AEs related to malignancies were reported in 4 subjects in the maraviroc group (1.4%) and 10 in the efavirenz group (3.3%). Three additional neoplasms were considered benign. Three events in the maraviroc group were considered related to the study drug: nasopharyngeal cancer, Hodgkin's disease, and diffuse large B-cell lymphoma. No event was considered related in the efavirenz group. Adverse events related to malignancies resulted in discontinuation in 3 instances in the maraviroc group and 4 in the efavirenz group. Adjusted for exposure, the incidence rate for maraviroc and efavirenz, respectively, was 1.0 and 2.4 events/100 years of exposure.

There were fewer Category C AIDS related events in the maraviroc group (2.5%) compared to the efavirenz group (3.3%). The main reason for this imbalance was a higher incidence of pulmonary tuberculosis in the efavirenz group. Adjusted for exposure, the incidences in the maraviroc group and the efavirenz group were 1.8 and 2.4/100 years, respectively.

Lipid changes were lower with maraviroc as compared to efavirenz. Liver enzymes were raised more frequently in the efavirenz group. Rates of laboratory abnormalities (including liver inflammation) did not differ between the treatment arms. No significant differences were found in other laboratory findings.

Statistical methodology

The concerns relating to the statistical methodology of the submitted study, such as the impact of multiplicity and post hoc analysis, were raised by the clinical evaluator. The sponsor provided their arguments in the response to the CER. The evaluator's concerns and sponsor's response in relation to statistical issues were reviewed by an external statistician.

In summary, the statistician is of the view that the methodological problems generated by multiplicity in this particular instance are considered at the low level of concern, and in this unusual instance where a subgroup analysis is based on a more sensitive assay (ESTA), multiplicity is not on its own a reason for rejection of the application. The available statistical evidence suggests that maraviroc is either non-inferior to efavirenz or

narrowly inferior to efavirenz. These statistical results would need to be considered in conjunction with background clinical knowledge.

Risk management plan

The RMP Version 1.6, dated 30 September 2010, has been reviewed by the Office of Product Review (OPR). The sponsor has adequately addressed all OPR recommendations raised during the evaluation of the RMP Version 1.6. The sponsor has submitted an updated EU-RMP (Version 1.7, dated October 2011) with an Australian Specific Annex as Annex 8. The RMP evaluator recommends that if this application is approved, the following specific condition of registration should be applied: *'the Risk Management Plan Version 1.7, dated October 2011, with an Australian Specific Annex (ASA) as Annex 8, must be implemented'*.

Risk-benefit analysis

Benefits

Based on the submitted data, the benefits associated with maraviroc BID treatment in treatment naïve patients infected with CCR5 tropic HIV-1 including the followings:

Non-inferior efficacy in the CCR5 tropic population identified by ESTA

The primary efficacy analysis with the OTA at Week 48 demonstrated non-inferiority only for VL < 400 copies/mL and only in the FAS. Efficacy was later re-analysed based on the CCR5 tropic population identified by ESTA. Of the 721 subjects in both arms of the study with virus originally classified as CCR5 at the screening, 106 (48 in the maraviroc group and 58 efavirenz group) were excluded from the re-analysis as they were identified as D/M tropic or X4 tropic by ESTA. The re-analysis supported the non-inferiority of maraviroc over efavirenz at Week 48 based on VL < 400 and VL < 50 copies/mL, however, non-inferiority was not demonstrated for the efficacy analysis at Week 96. Efficacy at Week 240 in terms of VL < 50 copies/mL and $CD4^+$ cell count appears to be well maintained.

Better tolerability and better $CD4^+$ cell gain

In general, the safety profile of maraviroc in treatment naïve patients was not different from the already known safety profile in treatment experienced patients. When compared to efavirenz, maraviroc demonstrated a better safety profile with respect to discontinuations due to AEs and with respect to lipid profile (cholesterol, LDL, and triglycerides). Better lipid profile is considered an advantage, especially for HIV patients with cardiovascular and metabolic co-morbidities. Importantly, no increased risk in Category C events or AIDS defining conditions has been numerically demonstrated.

Risks

The risks associated with maraviroc BID treatment in treatment naïve patients infected with CCR5 tropic HIV-1 include:

Higher risk of virologic failure and resistance development to backbone agents

Virological failure was much more common with maraviroc than with efavirenz. The number of discontinuations due to lack of efficacy was 2-3 times higher with maraviroc, and around 3-4 times as many patients in the maraviroc group developed resistance to the NRTI backbone treatment, in particular to lamivudine.

Tropism switch and clinical significance of the tropism change

Based on the subgroup analyses, it appears that maraviroc treatment failure may increase the risk of selection of non-CCR5 tropic virus. The currently available data did not indicate an association between tropism change and adverse clinical outcome. It is acknowledged that the submitted studies were not specifically designed to show individual responses to tropism change; the impact of tropism change (from CCR5 tropic to X4 tropic) on clinical outcomes, such as risk for malignancy and Category C infections, will need to be studied at longer term and in larger populations before a firm conclusion can be made.

Limitation with the ESTA

The commercially available ESTA requires a VL of at least 1,000 copies/mL, which may limit the early detection of X4-using virus. The length of time required for ESTA turnaround and the cost of the assay may be a problem in clinical practice.

Product Information

Product Information has been thoroughly reviewed by the clinical evaluator, and a draft PI incorporating relevant changes should be submitted. Further changes to the PI may be required after the Advisory Committee on Prescription Medicines (ACPM) discussion. Details of these are beyond the scope of this AusPAR.

Proposed action

The Delegate is of the opinion that the benefits and risks balance is favourable for the use of maraviroc (Celsentri), in combination with lamivudine 150 mg/zidovudine 300 mg, for treatment naïve adult patients infected with only CCR5 tropic HIV-1, provided that the *Indication* is qualified with appropriate information and the RMP as agreed with OPR is properly implemented.

Pending the advice from the ACPM, the Delegate proposes the approval of Celsentri, in combination with other antiretroviral medicinal products, for treatment naïve adult patients infected with only CCR5 tropic HIV-1, with the following points being considered when initiating the therapy:

- Adult patients infected with only CCR5 tropic HIV-1 should use Celsentri.
- CCR5 tropism should be confirmed using a highly sensitive tropism assay prior to initiation of Celsentri therapy. Outgrowth of pre-existing, low-level CXCR4 or D/M tropic HIV-1 not detected by tropism testing at screening has been associated with virologic failure on Celsentri.
- Celsentri is not recommended in patients infected with D/M or CXCR4 tropic HIV-1.
- In treatment naïve subjects, more subjects treated with Celsentri experienced virologic failure and developed lamivudine resistance compared to efavirenz.
- The safety and efficacy of Celsentri have not been established in paediatric patients.

Conditions of registration should include:

- Submission of the reports of ongoing studies.
- RMP Version 1.7, dated October 2011, with an Australian Specific Annex as Annex 8, must be implemented.

Advice requested from ACPM

The Delegate sought advice from ACPM specifically on the following aspects:

- Based on the efficacy analyses discussed above, is ACPM of the view that the non-inferiority of maraviroc BID compared to efavirenz QD, each in combination with lamivudine 150 mg/zidovudine 300 mg BID, is demonstrated in treatment naïve patients infected with CCR5 tropic HIV-1?
- Is ACPM of the view that the post hoc efficacy re-analysis based on ESTA assay is valid to support the extension of the indication to treatment naïve patients infected with CCR5 tropic HIV-1?
- Is ACPM of the view that the better safety profile of maraviroc (300 mg BID) outweighs the risk of treatment failure and resistance development to the backbone antiretroviral agents?

Response from sponsor

The sponsor provided comments on matters addressed to ACPM by the Delegate and on other matters raised in the Delegate's overview. Statements from four specialists (experts) in the field of HIV medicine were also provided and comments from these were referred to in the sponsor's response.

Efficacy results at Weeks 48, 96 and 240 in Study A4001026

Non-inferiority of maraviroc versus efavirenz is demonstrated by the definitive ESTA analysis of both co-primary endpoints (< 400 and < 50 copies/mL) at the pre-specified primary time point (Week 48) (Delegate concurs) with low concern for issues of multiplicity (statistical evaluator concurs). The 96 Week A4001026 data extend and reinforce the safety and efficacy results observed at Week 48. The analyses at both 48 and 96 Weeks showed only small differences between maraviroc and efavirenz in the proportions of subjects achieving VL < 50 copies/mL.[20] Data through 240 Weeks for the treatment naïve Study A4001026 provided useful information on the long term efficacy and safety of maraviroc and are the longest term clinical study efficacy data available for maraviroc. The percentage of subjects with a VL < 50 copies/mL at Weeks 48, 96 and 240 is shown in Table 15 for subjects with R5 virus at screening determined by the Trofile assay ('All subjects ') and by ESTA ('ESTA R5 subjects').

Table 15. Subjects with VL < 50 copies/mL at Weeks 48, 96 and 240 in Study A4001026

Number (%) of Subjects	MVC (300 mg BID)	EFV (600 mg QD)
ESTA R5 Subjects	**N=311**	**N=303**
Week 48	214 (68.8)	210 (69.3)
Week 96	184 (59.2)	189 (62.4)
Week 240	158 (50.8)	139 (45.9)
All Subjects	**N=360**	**N=361**
Week 48	236 (65.6)	253 (70.1)
Week 96	206 (57.2)	225 (62.3)
Week 240	176 (48.9)	165 (45.7)

Missing data = failure. N=Number of subjects in the treatment group in the indicated population used to calculate the percentage. Study A4001026, Full Clinical Study Report, Tables 14.2.1.1.1, 14.2.1.1.2, and 14.2.1.1.3 (Module 5.3.5.1)

As shown in Table 15, at Week 240, VL < 50 copies/mL was observed for slightly more ESTA R5 subjects in the maraviroc BID treatment group (158/311, 50.8%) versus the efavirenz QD treatment group (139/303, 45.9%). Results were qualitatively the same and quantitatively similar in all subjects enrolled, irrespective of the ESTA R5 assay: maraviroc BID (176/360, 48.9%) and efavirenz QD (165/361, 45.7%).

[20] Sierra-Madero J, Di Perri G, Wood R et al. Efficacy and safety of maraviroc versus efavirenz, both with zidovudine/lamivudine: 96-week results from the MERIT study. HIV Clin Trials. 2010;11(3):125-32.

Change from baseline in $CD4^+$ count by visit (LOCF) for ESTA R5 subjects was captured as a numerical advantage for the maraviroc BID treatment group over the efavirenz QD treatment group as early as the first study visit (Week 2; Study A4001026 240 week clinical study report). This advantage (approximately 25-30 cells/μL) was maintained across all subsequent visits. At Week 240, the mean increase from baseline in $CD4^+$ count for the maraviroc BID group was 292.9 cells/μL and 270.6 cells/μL for the efavirenz QD group. This result is meaningful to clinicians and an expert has noted, *'..maraviroc demonstrates a significant $CD4^+$ count advantage compared to efavirenz, reinforcing its benefit in these patient groups, where there are fewer treatment options due to the coexisting conditions.'*

Safety

As noted by the Delegate and the clinical evaluator (initial and final evaluation reports), maraviroc 300 mg BID demonstrated a better safety profile than efavirenz 600 mg OD with respect to discontinuations due to AEs and with respect to lipid profile (cholesterol, LDL and triglycerides). Discontinuations due to AEs, serious AEs and Grade 3 or 4 AEs occurred with a lower frequency in the maraviroc 300 mg BID treatment group compared to the efavirenz 600 mg QD treatment group.

Importantly, long term data through 240 weeks demonstrated no evidence of an increase in Category C events; no increased risk of development of malignancy in patients who took maraviroc; and no new or unexpected safety signals were reported from this study, as noted by the Delegate. There were no observed adverse clinical or immunological consequences related to the emergence of CXCR4-using virus associated with virologic failure on maraviroc. Individuals switching tropism during maraviroc-containing therapy had good immunological outcomes and responded to subsequent therapy (Portsmouth *et al*. 2010[21]).

An expert states, *'The side effect profile in our patient experience is minimal – consisting of some nausea for 2-3 days after initiating therapy and spontaneously resolving.'*

The Delegate made the observation that the safety profile demonstrated in the treatment naïve patients aligned with that known for treatment experienced patients. The most recent PSUR that was submitted recently to the TGA continues to support a favourable safety profile for treatment experienced patients.

Viral resistance

In patients who develop resistance on the trial, the mutation that developed most commonly was that for lamivudine (M184V). The clinical significance of this mutation has been debated for years as this mutation leads to a less fit virus which is less pathogenic and most treatment guidelines suggest maintaining selection pressure for this mutation once it has been identified. The clinical evaluator conceded that the presence of the M184V mutation may not necessarily preclude continuing treatment with lamivudine.

Notably, of 4 efavirenz treated subjects who discontinued due to lack of efficacy, 3 subjects had virus that selected K103N (with resistance to efavirenz) and 1 of these 3 subjects also selected M184V, with resistance to lamivudine. Also, of the 4 efavirenz treated subjects with virologic failure at Week 96, 3 subjects selected NNRTI resistance-associated mutations (K103N, K103N/P225H and V106M); virus from the remaining subjects remained wild-type. There were no NRTI resistance-associated mutations selected.

The efficacy of rilpivirine in HIV-infected, treatment naïve subjects was demonstrated in two Phase III trials (C209 [ECHO] and C215 [THRIVE]) in which efavirenz was used as the

[21] Portsmouth SD, Lewis M, Craig C et al. Long Term Outcome of Individuals Experiencing a Phenotypic Switch in HIV-1 Co-receptor Use in the MERIT Study. Poster no. 104. Presented to the International HIV & Hepatitis Virus Drug Resistance Workshop and Curative Strategies; June 8-12,2010; Dubrovnik, Croatia

active comparator. Rilpirvirine was approved by the TGA for therapy of treatment naïve patients in December, 2011. As in Study A4001026, more subjects discontinued rilpivirine due to virologic failure; conversely, more subjects discontinued efavirenz due to AEs. Furthermore, subjects experiencing virologic failure on rilpivirine developed more NNRTI resistance-associated substitutions conferring more cross-resistance to the NNRTI class and had a higher likelihood of cross-resistance to all NNRTIs in the class than subjects who failed on efavirenz. [22,23,24]

An expert provides the following Australian clinical context: *'The use of an agent which may have demonstrated a higher risk of failure in clinical trials does not necessarily translate into a higher risk of failure in clinical practice: the key to treatment success is patient adherence'*.

Tropism

The sponsor agrees that CXCR4-using virus is more often seen in later stages of HIV infection and coincides with disease progression. However, the sponsor does not believe the evidence would concur with the assessment that maraviroc treatment puts patients at risk of more rapid disease progression with the selection of CXCR4-using virus. Tropism change was not seen in isolation but found in the context of M184V. It is likely that in later stages of HIV infection, CXCR4-using virus emerges as a result of progressive immune dysregulation rather than being a cause of it.[25]

Unlike natural disease progression which coincides with increasing CXCR4 use, the emergence of CXCR4-using virus during therapy with maraviroc has been shown to be reversible on withdrawal of maraviroc. Selective pressure from maraviroc will lead to the emergence of pre-existing CXCR4-using virus that then on cessation of maraviroc therapy will be replaced with CCR5-using virus. CCR5-using virus often rapidly outgrows CXCR4 virus suggesting the CCR5 tropic virus is indeed fitter than CXCR4-using virus.[26]

The emergence of CXCR4-using virus is less detrimental to patients than, for example, emergence of resistance to an NNRTI, which may disqualify several drugs from future use. Maraviroc is the only CCR5 inhibitor currently available, so there is currently no potential for a succession of entry inhibitor treatment. Furthermore, the potential clinical benefit for re-treatment with maraviroc on the reversion of the D/M phenotype after maraviroc withdrawal has not been explored.

Several Australian HIV clinical specialists have lent their opinion to this issue and they are of the view there is no extra concern over the development of CXCR4 virus. One of these expert states: '*the available data strongly suggest that CCR5 tropism reversion does occur following the withdrawal (or failure) of maraviroc therapy, and that the natural history is not altered significantly.'* It is regarded as a means for viral escape of drug-pressure and as such is comparable with conventional antiretroviral drugs; emergence of pre-existing viral species that are not susceptible to the antiretroviral therapy (ART). Commonly, a low percentage of patients develop conventional resistance using another agent, and this is no different to the percentage reported with maraviroc. These patients can be treated with

[22] Cohen CJ, Villanueva JA, Clotet B, et al. (on behalf of THRIVE study group). Rilpivirine versus EFV with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. Lancet 2011:378:229 -237
[23] Medical review(s): Centre for Drug Evaluation and Research – application number 202022Orig1s000.
[24] Molina JM, Cahn P, Grinsztein B, et al. (on behalf of the ECHO Study group). Rilpivirine versus EFV with tenofovir and emtricitabine in treatment-naïve adults infected with HIV-l (ECHO): a phase 3 randomised double blind active controlled trial. Lancet 2011;378:238-246.
[25] Ariën KK, Gali Y, El-Abdellati A, et al. Replicative fitness of CCR5-using and CXCR4-using human immunodeficiency virus type I biological clones. Virology. 2006;347:65-74.
[26] Westby M, Lewis M, Whitcomb J, et al. Emergence of CXCR4-using human immunodeficiency virus type 1 (HIV-l) variants in a minority of HIV-1-infected patients following treatment with the CCR5 antagonist maraviroc is from a pretreatment CXCR4-using virus reservoir. J Virol. 2006 May; 80(1 0):4909-20.

another regimen as currently the therapy landscape provides more treatment options, which is an ongoing critical need in the treatment of HIV infection as resistance development and tolerability are the key factors in switching therapy.

The concern over the impact of tropism change from CCR5 tropic to CXCR4 tropic in the development of malignancy or incidence of Category C events is speculative at this stage, as there is no evidence from the pivotal trial data to suggest this is the case. To evaluate these risks, longer term studies and larger populations would be required. Of note, the incidence of these events at Week 240 was 3.1% in the maraviroc arm versus 3.9% in the efavirenz arm with the majority of these being cases of tuberculosis. The incidence of non-Category C malignancies was also similar between groups.

Tropism testing

The OTA from Monogram Biosciences is the only tropism assay that has undergone prospective evaluation in the context of large registrational clinical studies. OTA, a phenotypic assay, supported the licensure of maraviroc in the US and EU for ART experienced (MOTIVATE[27]) patients who harbor R5 virus. An ESTA was subsequently developed and commercialised by Monogram Biosciences.[28] This assay supported the ART naïve indication granted in the US for patients with R5 virus. While ESTA is a modified or enhanced version of OTA, it has not been formally evaluated in large prospective clinical studies. Neither the OTA nor ESTA are FDA-approved assays; they are governed under the standards outlined in the US Clinical Laboratory Improvement Amendments (CLIA) of 1988.

An expert notes*: 'Virtually all naïve patients considering starting treatment will have an HIV VL over 1,000 copies and the decision to start treatment is rarely so urgent that the time required to obtain an assay result will be critical'*. However, recent advances in both laboratory methodologies to generate high quality V3 loop sequence data and bioinformatics algorithms has greatly advanced the clinical utility of genotypic tropism methods, and with reduced time for results (1-2 weeks inclusive, compared to 6-7 weeks for ESTA), have become the most practical means for tropism testing in Australia. As with HIV resistance testing, genotypic tropism testing provides a viable option for patient management and is currently being utilised by accredited laboratories in Australia. The Australian commentary on the DHHS Guidelines and the European Consensus Group on clinical management of tropism testing have recently included a recommendation for the use of genotypic tropism testing in their treatment guidelines.[29] An expert states, '*Given that baseline HIV drug resistance genotyping is standard in Australian centres including Royal Perth Hospital, and that results are routinely considered by clinicians when considering first-line therapy, the process of performing and interpreting a highly-sensitive CCR5 tropism assay does not represent a major challenge in routine clinical care*'.

A total of 859 screening samples from the MERIT trial were re-examined using ESTA and genotypic testing. Overall concordance between the two tests was 82.1%. Specificity and NPV were both high at 92.7% and 87.1% respectively (Swenson *et al*, 2011[30]). These methods performed similarly in predicting virological response to maraviroc, as illustrated in Table 16.

[27] MOTIVATE refers to the Phase II clinical trial Maraviroc versus Optimized Therapy in Viremic Antiretroviral Treatment-Experienced Patients.
[28] Reeves JD, Coakley E, Petropoulos CJ, Whitcomb JM. An enhanced-sensitivity Trofile HIV coreceptor tropism assay for selecting patients for therapy with entry inhibitors targeting CCR5: A review of analytical and clinical studies. *J Viral Entry* 2009;3:94-702.
[29] Vandekerckhove LPR, Wensing AMJ, Kaiser R, *et al*. European guidelines on the clinical management of HIV-1 tropism testing. *The Lancet Infectious Diseases*.20l l; 1 1(5):394-407
[30] Swenson LC, Mo T., Dong W. *et al*. Deep V3 sequencing for HIV type 1 tropism in treatment-naïve patients: A reanalysis of the MERIT trial of maraviroc. *Clin Infec Dis* 2011:53;732-742.

Table 16. Non-inferiority analysis between the maraviroc and efavirenz treatment arms.

Assay result	No. of patients with VR at 48 weeks, n/N (%)		Raw diff (MVC-EFV)	Stratified	
	MVC BID arm	EFV arm		Diff	97.5% LCB
G2P R5	210/312 (67.3)	217/316 (68.7)	-1.4	-1.5	-8.7
G2P non-R5	17/35 (48.6)	21/30 (70.0)	-21.4	-42.2	-60.7
ESTA R5	205/300 (68.3)	196/290 (67.6)	0.75	0.2	-7.2
ESTA non-R5	22/47 (46.8)	42/56 (75.0)	-28.2	-31.2	-48.9

Abbreviations: BID, twice-daily; EFV, efavirenz; ESTA, enhanced-sensitivity Trofile assay; G2P, geno2pheno; LCB, lower confidence bound; MVC, maraviroc; VR, virological response

The collective datasets described in the submission, as well as others, support the notion that the change from R5 to non-R5 (that is, dual-, mixed-, or X4 tropic) requires significant time (in the absence of therapy) or significant drug pressure (in the context of maraviroc-containing HAART). Nevertheless, the question arises if HIV tropism could change during the course of a screening evaluation period such that a tropism result based on a sample at time point "1" would not be relevant at time point "2".

Given the rapid turnaround time (1-2 weeks) with genotypic testing, and the data from natural history studies and analyses of virologic failures with maraviroc-containing HAART, changes in tropism during the testing period should not be a point of concern.

Spontaneous tropism changes (from R5 to non-R5 or vice-versa) were observed in approximately 10% of patients between screening and study baseline in the maraviroc clinical trials using the OTA; the turnaround time for Trofile is at least two weeks from the point of sample receipt at the laboratory. In an effort to characterise these discordant, intra-patient samples, population-based and "deep" sequencing analyses of the HIV envelope V3 loop were performed. Maraviroc recipients in the MERIT, MOTIVATE and A4001029 studies who spontaneously changed tropism readout (n = 53) or did not change (n = 72 random samples) by the OTA between screening and baseline (approximately 4-8 weeks) were evaluated. Tropism of the V3 loop sequences was inferred by "geno2pheno" algorithm.

In the majority of cases, the prevalence of non-CCR5 usage inferred from "deep" sequencing was stable over the short term between screening and baseline. Where apparent phenotypic tropism changes from R5 to non-R5 occurred, non-R5 virus was generally detectable at the screening time point by genotype coupled with relatively small increases in non-R5 virus by the baseline time point. These findings are consistent with the authors' conclusion that small variations in CXCR4-using HIV populations around the phenotypic assay detection limit, rather than co-receptor switch (that is, a recent evolutionary event), contributed to apparent changes in Trofile readouts.[31]

Product Information

The proposed INDICATION is:

Celsentri, in combination with other antiretroviral medicinal product, is indicated for adult patients infected with CCR5 tropic HIV-1.

The use of other active agents with Celsentri is associated with a greater likelihood of treatment response.

The Delegate has recommended the approval of this indication and proposed several points for inclusion in the PI to be considered before the initiation of therapy. As these points are found in the *Usage* section of the US PI, which does not exist in the Australian PI, the sponsor believes it appropriate to incorporate them into the *Dosage and Administration* section following the existing statement *'The following points should be considered when initiating therapy with Celsentri'*.

[31] Brumme CJ, Dong W, Chan D, *et al*. Short-term variation of HIV tropism readouts in the absence of CCR5-antagonists. *J Int AIDS Soc* 2010; 13(Suppl. 4): O9.

Details of other revisions to the PI and CMI are beyond the scope of this AusPAR.

Benefit-risk assessment - conclusion

The Delegate and the clinical evaluator on consideration of the benefits and risk balance find in favour of approving the extension of *Indication* for Celsentri to include treatment naïve patients. The sponsor welcomes this recommendation given the difficult to treat area of HIV therapy, where regimen selection requires individualisation based on a number of factors.

An expert offers his opinion from the Australian HIV Specialist view, *'I would agree with the view the benefits of approving maraviroc for first-line treatment outweigh the risks, and that current clinical practice (which is increasingly interested in early treatment) and laboratory support (which now provides clinically relevant V3 genotyping results using highly sensitive assay methods) provide the optimal conditions for maraviroc treatment to be utilised in Australia.'*

The sponsor agrees to the conditions of registration proposed by the Delegate; submission of reports of ongoing studies and implementation of the RMP (v 1.7), including the Australia Specific Annex.

Advisory committee considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered this product to have an overall positive benefit-risk profile for the following indication**:**

For treatment naïve patients infected with only CCR5 tropic HIV-1.

In making this recommendation the ACPM carefully considered the evidence that use in treatment naïve patients efficacy must be balanced with the safety risks associated with reversible neurological toxicity and the permanent risk of the emergence of resistance; hence treatment must be limited to patients with the highly sensitive phenotypic CCR5 tropic virus.

In addition, the ACPM advised that CCR5 tropism should be confirmed using a highly sensitive tropism assay prior to initiation of Celsentri therapy and noted that outgrowth of pre-existing low-level CXCR4 or D/M tropic HIV-1 that is not detected by tropism testing at screening has been associated with increased virologic failure with this product. The ACPM cautioned that until a validated widely available highly sensitive diagnostic assay test was available for CCR5 tropic virus, it remained challenging for clinicians to target this very specific population group for this indication.

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following in a higher profile position than dosage and administration sections as proposed by the sponsor.

- statements in the appropriate *Clinical Trials*, *Precautions* or *Contraindications* sections of the PI and CMI to ensure:
  - the product be limited to use in adult patients infected only with only CCR5 and is not recommended in patients infected with CXCR4 tropic HIV-1 or D/M tropic virus, and that safety or efficacy has not been established in children.
  - that CCR5 should be confirmed using a highly sensitive tropism assay.

  - awareness that treatment naïve patients using this product are more likely to experience treatment failure and develop lamivudine resistance when compared to efavirenz.
  - the accurate reflection and awareness of the risk of treatment failure and resistance development to the backbone agents. These statements must have a higher profile than those in the proposed documents with consideration given to inclusion of clearer tabulation of treatment failure and the percentage of patients with adverse event, naming the higher percentage of patients had treatment failure in maraviroc (twice daily dosing group versus higher percentage of patients experienced adverse event in the efavirenz, once daily dosage group). Highlight that the only backbone therapy used in the studies was zidovudine and lamivudine.

- statements in the *Adverse events / Side effects* sections to adopt a similar approach to the FDA with statements to describe the severe rash followed by generalised immune disorders, as well as cardiac dysfunction and hepatocellular dysfunction, as reported in the PSUR.

The ACPM agreed with the Delegate on the proposed conditions of registration.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided, would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Celsentri tablets containing maraviroc 150 mg and 300 mg for the following new indication:

> *Celsentri, in combination with other antiretroviral medicinal products, is indicated for treatment experienced adult patients infected with only CCR5-tropic HIV-1.*

The full indications are now:

> *Celsentri, in combination with other antiretroviral medicinal products, is indicated for treatment experienced adult patients infected with only CCR5-tropic HIV-1.*
>
> *The use of other active agents with Celsentri is associated with a greater likelihood of treatment response.*

This approval is based on the evaluation of the information and data provided with the original letter of application and with any subsequent correspondence and submissions relating to the application.

Specific conditions of registration applying to these goods

The implementation in Australia of maraviroc RMP version 1.7, October 2011 with an Australian specific Annex as Annex 8, and any subsequent revisions, as agreed with the TGA and its OPR.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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